moving from start (N-terminus or 5') to end (C-terminus or 3'), such that for an alignment that extends to p monomers (where p>x) there are p-x+1 such windows, each window has at least xy identical aligned monomers, where: x is slected from 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100, 150, 200; y is selected from 0.50, 0.60, 0.70, 0.75, 0.80, 0.85, 0.90, 0.91, 0.92, 0.93, 0.94, 0.95, 0.96, 0.97, 0.98, 0.99; and if xy is not an integer then it is rounded up to the nearest integer. The preferred pairwise alignment algorithm is the Needleman-Wunsch global alignment algorithm [Needlman &Wunsch (1970) J. Mol. Biol. 48, 443-453], using default parameters (e.g., with Gap opening penalty = 10.0, and with Gap extension penalty = 0.5, using the EBLOSUM62 scoring matrix). This algorithm is conveniently implemented in the needle tool in the EMBOSS package [Rice et al. (2000) Trends Genet. 16:276-277].

The nucleic acids and polypeptides of the inention may additionally have further sequences to the N-terminus/5' and/or C-terminus/3' of these sequences (a) to (d).

All of the Gram positive bacterial sequences referenced herein are publicly available through PubMed on GenBank.

Streptococcus pneumoniae Adhesin Island Sequences

As discussed above, a S. pneumoniae AI sequence is present in the TIGR4 S. pneumoniae genome. Examples of S. pneumoniae AI sequences are set forth below.

20 SrtD (Sp0468) is a sortase. An example of an amino acid sequence of SrtD is set forth in SEQ ID NO: 80.

SEQ ID NO: 80

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MSRTKLRALLGYLLMLVACLIPIYCFGQMVLQSLGQVKGHATFVKSMTTEMYQEQQNHSLAYNQRLASQNRIVDP FLAEGYEVNYQVSDDPDAVYGYLSIPSLEIMEPVYLGADYHHLGMGLAHVDGTPLPLDGTGIRSVIAGHRAEPSH VFFRHLDQLKVGDALYYDNGQEIVEYQMMDTEIILPSEWEKLESVSSKNIMTLITCDPIPTFNKRLLVNFERVAV YQKSDPQTAAVARVAFTKEGQSVSRVATSQWLYRGLVVLAFLGILFVLWKLARLLRGK

SrtC (Sp0467) is a sortase. An example of an amino acid sequence of SrtC is set forth in SEQ ID NO: 81.

30 **SEQ ID NO: 81**

MSRYYYRIESNEVIKEFDETVSQMDKAELEERWRLAQAFNATLKPSEILDPFTEQEKKKGVSEYANMLKVHERIG YVEIPAIDQEIPMYVGTSEDILQKGAGLLEGASLPVGGENTHTVITAHRGLPTAELFSQLDKMKKGDIFYLHVLD QVLAYQVDQIVTVEPNDFEPVLIQHGEDYATLLTCTPYMINSHRLLVRGKRIPYTAPIAERNRAVRERGQFWLWL LLGAMAVILLLLYRVYRNRRIVKGLEKQLEGRHVKD

SrtB (SP0466) is a sortase. An example of an amino acid sequence of SrtB is set forth in SEQ ID NO: 82.

SEQ ID NO: 82

MAVMAYPLVSRLYYRVESNQQIADFDKEKATLDEADIDERMKLAQAFNDSLNNVVSGDPWSEEMKKKGRAEYARM LEIHERMGHVEIPVIDVDLPVYAGTAEEVLQQGAGHLEGTSLPIGGNSTHAVITAHTGLPTAKMFTDLTKLKVGD KFYVHNIKEVMAYQVDQVKVIEPTNFDDLLIVPGHDYVTLLTCTPYMINTHRLLVRGHRIPYVAEVEEEFIAANK LSHLYRYLFYVAVGLIVILLWIIRRLRKKKKQPEKALKALKAARKEVKVEDGQQ

Sp0465 is a hypothetical protein. An example of an amino acid sequence of Sp0465 is set forth in SEQ ID NO: 83.

SEQ.DINO. 1835 05 / 27235

MFLPFLSASLYLQTHHFIAFPNRQSYLLRETRKSHFFLIHHPF

RrgC (SP0464) is a cell wall surface anchor family protein. RrgC contains a sortase substrate motif VPXTG (SEQ ID NO: 137), shown in italics in SEQ ID NO: 84.

SEQ ID NO: 84

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MISRIFFVMALCFSLVWGAHAVQAQEDHTLVLQLENYQEVVSQLPSRDGHRLQVWKLDDSYSYDDRVQIVRDLHS WDENKLSSFKKTSFEMTFLENQIEVSHIPNGLYYVRSIIQTDAVSYPAEFLFEMTDQTVEPLVIVAKKTDTMTTK VKLIKVDQDHNRLEGVGFKLVSVARDVSEKEVPLIGEYRYSSSGQVGRTLYTDKNGEIFVTNLPLGNYRFKEVEP LAGYAVTTLDTDVQLVDHQLVTITVVNQKLPRGNVDFMKVDGRTNTSLQGAMFKVMKEESGHYTPVLQNGKEVVV TSGKDGRFRVEGLEYGTYYLWELQAPTGYVQLTSPVSFTIGKDTRKELVTVVKNNKRPRID*VPDTG*EETLYILML VAILLFGSGYYLTKKPNN

RrgB (Sp0463) is a cell wall surface anchor protein. RrgB contains a sortase substrate motif IPXTG (SEQ ID NO: 133), shown in italics in SEQ ID NO: 85.

SEQ ID NO: 85

MKSINKFLTMLAALLLTASSLFSAATVFAAGTTTTSVTVHKLLATDGDMDKIANELETGNYAGNKVGVLPANAKE IAGVMFVWTNTNNEIIDENGQTLGVNIDPQTFKLSGAMPATAMKKLTEAEGAKFNTANLPAAKYKIYEIHSLSTY VGEDGATLTGSKAVPIEIELPLNDVVDAHVYPKNTEAKPKIDKDFKGKANPDTPRVDKDTPVNHQVGDVVEYEIV TKIPALANYATANWSDRMTEGLAFNKGTVKVTVDDVALEAGDYALTEVATGFDLKLTDAGLAKVNDQNAEKTVKI TYSATLNDKAIVEVPESNDVTFNYGNNPDHGNTPKPNKPNENGDLTLTKTWVDATGAPIPAGAEATFDLVNAQTG KVVQTVTLTTDKNTVTVNGLDKNTEYKFVERSIKGYSADYQEITTAGEIAVKNWKDENPKPLDPTEPKVVTYGKK FVKVNDKDNRLAGAEFVIANADNAGQYLARKADKVSQEEKQLVVTTKDALDRAVAAYNALTAQQQTQQEKEKVDK AQAAYNAAVIAANNAFEWVADKDNENVVKLVSDAQGRFEITGLLAGTYYLEETKQPAGYALLTSRQKFEVTATSY SATGQGIEYTAGSGKDDATKVVNKKITIPQTGGIGTIIFAVAGAAIMGIAVYAYVKNNKDEDQLA

RrgA (Sp0462) is a cell wall surface anchor protein. RrgA contains a sortase substrate motif YPXTG (SEQ ID NO: 186), indicated in italics in SEQ ID NO: 86.

SEQ ID NO: 86

MLNRETHMKKVRKIFQKAVAGLCCISQLTAFSSIVALAETPETSPAIGKVVIKETGEGGALLGDAVFELKNNTDG
TTVSQRTEAQTGEAIFSNIKPGTYTLTEAQPPVGYKPSTKQWTVEVEKNGRTTVQGEQVENREEALSDQYPQTGT
YPDVQTPYQIIKVDGSEKNGQHKALNPNPYERVIPEGTLSKRIYQVNNLDDNQYGIELTVSGKTVYEQKDKSVPL
DVVILLDNSNSMSNIRNKNARRAERAGEATRSLIDKITSDSENRVALVTYASTIFDGTEFTVEKGVADKNGKRLN
DSLFWNYDQTSFTTNTKDYSYLKLTNDKNDIVELKNKVPTEAEDHDGNRLMYQFGATFTQKALMKADEILTQQAR
QNSQKVIFHITDGVPTMSYPINFNHATFAPSYQNQLNAFFSKSPNKDGILLSDFITQATSGEHTIVRGDGQSYQM
FTDKTVYEKGAPAAFPVKPEKYSEMKAAGYAVIGDPINGGYIWLNWRESILAYPFNSNTAKITNHGDPTRWYYNG
NIAPDGYDVFTVGIGINGDPGTDEATATSFMQSISSKPENYTNVTDTTKILEQLNRYFHTIVTEKKSIENGTITD
PMGELIDLQLGTDGRFDPADYTLTANDGSRLENGQAVGGPQNDGGLLKNAKVLYDTTEKRIRVTGLYLGTDEKVT
LTYNVRLNDEFVSNKFYDTNGRTTLHPKEVEQNTVRDFPIPKIRDVRKYPEITISKEKKLGDIEFIKVNKNDKKP
LRGAVFSLQKQHPDYPDIYGAIDQNGTYQNVRTGEDGKLTFKNLSDGKYRLFENSEPAGYKPVQNKPIVAFQIVN
GEVRDVTSIVPQDIPAGYEFTNDKHYITNEPIPPKREYPRTGGIGMLPFYLIGCMMMGGVLLYTRKHP

RlrA (Sp0461) is a transcriptional regulator. An example of an amino acid sequence for RlrA is set forth in SEQ ID NO: 87.

45 **SEO ID NO: 87**

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MLNKYIEKRITDKITILNILLDIRSIELDELSTLTSLQSKSLLSILQELQETFEEELTFNLDTQQVQLIEHHSHQ
TNYYFHQLYNQSTILKILRFFLLQGNQSFNEFTQKEYISIATGYRVRQKCGLLLRSVGLDLVKNQVVGPEYRIRF
LIALLQFHFGIEIYDLNDGSMDWVTHMIVQSNSQLSHELLEITPDEYVHFSILVALTWKRREFPLEFPESKEFEK
LKNLFMYPILMEHCQTYLEPHANMTFTQEELDYIFLVYCSANSSFSKDKWNQEKKTHTIQLILQHTRGKHLLSKF
KNILGNDISNSLSFLTALTFLTRTFLFGLQNLVPYYNYYEHYGIESDKPLYHISKAIVQEWMTEQKIEGVIDQHR
LYLFSLYLTETIFSSLPAIPIFIILNNQADVNLIKSIILRNFTDKVASVTGYNILISPPPSEEHLTEPLIIITTK
EYLPYVKKQYPKGKHHFLTIALDLHVSQQRLIYQTIVDIRKEAFDKRVAMIAKKAHYLL

As discussed above, a *S. pneumoniae* AI sequence is present in the *S. pneumoniae* strain 670 genome. Examples of *S. pneumoniae* AI sequences are set forth below.

Orfi_670 is a transposase. An example of an amino acid sequence of orfi_670 is set forth in SEQ ID NO: 171.

SEQ ID NO: 171

MEHINHTTLLIGIKDKNITLNKAIQHDTHIEVFATLDYHPPKCKHCKGKQIKYDFQKPSKIPFIEIGGFPSLIHL

KKRRFQCKSCRKVTVAETTLVQKNCQISEMVRQKIAQLLLNREALTHIASKLAISTSTSTVYRKLKQFHFQEDYT
TLPEILSWDEFSYQKGKLAFIAQDFNTKKIMTILDNRRQTTIRNHFFKYSKEARKKVKVVTVDMSGSYIPLIKKL
FPNAKIVLDRFHIVQHMSRALNQTRINIMKQFDDKSLEYRALKYYWKFILKDSRKLSLKPFYARTFRETLTPREC
LKKIFTLVPELKDYYDLYQLLIFHLQEKNTDQFWGLIQDTLPHLNRTFKTTLSTFICYKNYITNAIELPYSNAKL
EATNKLIKDIKRNAFGFRNFENFKKRIFIALNIKKERTKFVLSRA

Orf2_670 is a transcriptional regulator. An example of an amino acid sequence of Orf2_670 is set forth in SEQ ID NO: 172.

SEQ ID NO: 172

MLNKYIEKRITDKITILNILLDIRSIELDELSTLTSLQSKSLLSILQELQETFEEELTFNLDTQQVQLIEHHSHQ
TNYYFHQLYNQSTILKILRFFLLQGNQSFNEFTQKEYISIATGYRVRQKCGLLLRSVGLDLVKNQVVGPEYRIRF
LIALLQFHFGIEIYDLNDGSMDWVTHMIVQSNSQLSHELLEITPDEYVHFSILVALTWKRREFPLEFPESKEFEK
LKNLFMYPILMEHCQTYLEPHANMTFTQEELDYIFLVYCSANSSFSKDKWNQEKKTHTIQLILQHTRGKHLLSKF
KNILGNDISNSLSFLTALTFLTRTFLFGLQNLVPYYNYYEHYGIESDKPLYHISKAIVQEWMTEQKIEGVIDQHR
LYLFSLYLTETIFSSLPAIPIFIILNNQADVNLIKSIILRNFTDKVASVTGYNILISPPPSEEHLTEPLIIITTK
EYLPYVKKQYPKGKHHFLTIALDLHVSQQRLIYQTIVDIRKEAFDKRVAMIAKKAHYLL

Orf3_670 is a cell wall surface anchor family proten. An example of an amino acid sequence of Orf3_670 is set forth in SEQ ID NO: 173.

SEQ ID NO: 173

25 MINRETHMKKVRKIFQKAVAGLCCISQLTAFSSIVALAETPETSPAIGKVVIKETGEGGALLGDAVFELKNNTDG
TTVSQRTEAQTGEAIFSNIKPGTYTLTEAQPPVGYKPSTKQWTVEVEKNGRTTVQGEQVENREEALSDQYPQTGT
YPDVQTPYQIIKVDGSEKNGQHKALNPNPYERVIPEGTLSKRIYQVNNLDDNQYGIELTVSGKTTVETKEASTPL
DVVILLDNSNSMSNIRHNHAHRAEKAGEATRALVDKITSNPDNRVALVTYGSTIFDGSEATVEKGVADANGKILN
DSALWTFDRTTFTAKTYNYSFLNLTSDPTDIQTIKDRIPSDAEELNKDKLMYQFGATFTQKALMTADDILTKQAR
PNSKKVIFHITDGVPTMSYPINFKYTGTTQSYRTQLNNFKAKTPNSSGILLEDFVTWSADGEHKIVRGDGESYQM
FTKKPVTDQYGVHQILSITSMEQRAKLVSAGYRFYGTDLYLYWRDSILAYPFNSSTDWITNHGDPTTWYYNGNMA
QDGYDVFTVGVGVNGDPGTDEATATRFMQSISSSPDNYTNVADPSQILQELNRYFYTIVNEKKSIENGTITDPMG
ELIDFQLGADGRFDPADYTLTANDGSSLVNNVPTGGPQNDGGLLKNAKVFYDTTEKRIRVTGLYLGTGEKVTLTY
NVRLNDQFVSNKFYDTNGRTTLHPKEVEKNTVRDFPIPKIRDVRKYPEITIPKEKKLGEIEFIKINKNDKKPLRD
AVFSLQKQHPDYPDIYGAIDQNGTYQNVRTGEDGKLTFKNLSDGKYRLFENSEPAGYKPVQNKPIVAFQIVNGEV
RDVTSIVPQDIPAGYEFTNDKHYITNEPIPPKREYPRTGGIGMLPFYLIGCMMMGGVLLYTRKHP

Orf4_670 is a cell wall surface anchor family protein. An example of an amino acid sequence of orf4_670 is set forth in SEQ ID NO: 174.

40 SEQ ID NO: 174

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 $\label{thm:label_tasslesaatvfaadnvstapdavtktltikkllseddlktwdtngpkgydgtqsslk dltgvvaeeipnvyfelqkynltdgkekenlkddskwttvhgglttkdglkietstlkgvyriredrtkttyvgp ngqvltgskavpalvtlplvnnngtvidahvfpknsynkpvvdkriadtlnyndqnglsigtkipyvvnttipsn atfatsfwsdemtegltynedvtitlnnvamdqadyevtkgnngfnlklteaglakingkdadqkiqitysatln slavadipesndityhygnhqdhgntpkptkpnngqitvtktwdsqpapegvkatvqlvnaktgekvgapvelse nnwtytwsgldnsieykveeeyngysaeytveskgklgvknwkdnnpapinpeeprvktygkkfvkvdqkdtrle naqfvvkkadsnkyiafkstaqqaadekaaatakqkldaavaaytnaadkqaaqalvdqaqqeynvaykeakfgy vevagkdeamvltsntdgqfqisglaagtykleeikapegfakiddvefvvgagswnqgefnylkdvqkndatkv vnkkitipqtggigtiifavagaaimgiavyayvknnkdedqla$

Orf5_670 is a cell wall surface anchor family protein. An example of an amino acid sequence of orf5_670 is set forth in SEQ ID NO: 175.

SEO ID NO: 175

MTMQKMQKMISRIFFVMALCFSLVWGAHAVQAQEDHTLVLQLENYQEVVSQLPSRDGHRLQVWKLDDSYSYDDRV QIVRDLHSWDENKLSSFKKTSFEMTFLENQIEVSHIPNGLYYVRSIIQTDAVSYPAEFLFEMTDQTVEPLVIVAK

KTDTMTTKVKELKVDQDHNRLEGVGFKEVSVARDGSEKEVPLIGEYRYSSSGQVGRTLYTDKNGEIFVTNLPLGN YRFKEVEPLAGYAVTTLDTDVQLVDHQLVTITVVNQKLPRGNVDFMKVDGRTNTSLQGAMFKVMKEESGHYTPVL QNGKEVVVTSGKDGRFRVEGLEYGTYYLWELQAPTGYVQLTSPVSFTIGKDTRKELVTVVKNNKRPRIDVPDTGE ETLYILMLVAILLFGSGYYLTKKPNN

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Orf6_670 is a sortase. An example of an amino acid sequence of orf6_670 is set forth in SEQ ID NO: 176.

SEQ ID NO: 176

MLIKMVKTKKQKRNNLLLGVVFFIGMAVMAYPLVSRLYYRVESNQQIADFDKEKATLDEADIDERMKLAQAFNDS
LNNVVSGDPWSEEMKKKGRAEYARMLEIHERMGHVEIPVIDVDLPVYAGTAEEVLQQGAGHLEGTSLPIGGNSTH
AVITAHTGLPTAKMFTDLTKLKVGDKFYVHNIKEVMAYQVDQVKVIEPTNFDDLLIVPGHDYVTLLTCTPYMINT
HRLLVRGHRIPYVAEVEEEFIAANKLSHLYRYLFYVAVGLIVILLWIIRRLRKKKKQPEKALKALKAARKEVKVE
DGQQ

15 Orf7 ID NO: 177.

Orf7_670 is a sortase. An example of an amino acid sequence of orf7_670 is set forth in SEQ

SEO ID NO: 177

VSRYYYRIESNEVIKEFDETVSQMDKAELEERWRLAQAFNATLKPSEILDPFTEQEKKKGVSEYANMLKVHERIG
YVEIPAIDQEIPMYVGTSEEILQKGAGLLEGASLPVGGENTHTVVTAHRGLPTAELFSQLDKMKKGDVFYLHVLD
QVLAYQVDQILTVEPNDFEPVLIQHGEDYATLLTCTPYMINSHRLLVRGKRIPYTAPIAERNRAVRERGQFWLWL
LLAALVMILVLSYGVYRHRRIVKGLEKQLEEHHVKG

Orf8_670 is a sortase. An example of an amino acid sequence of orf8_670 is set forth in SEQ ID NO: 178.

25 SEQ ID NO: 178

MSKÄKLQKLLGYLLMLVALVIPVYCFGQMVLQSLGQVKGHEIFSESVTADSYQEQLQRSLDYNQRLDSQNRIVDP FLAEGYEVNYQVSDDPDAVYGYLSIPSLEIMEPVYLGADYHHLAMGLAHVDGTPLPVEGKGIRSVIAGHRAEPSH VFFRHLDQLKVGDALYYDNGQEIVEYQMMDTEIILPSEWEKLESVSSKNIMTLITCDPIPTFNKRLLVNFERVAV YQKSDPQTAAVARVAFTKEGQSVSRVATSQWLYRGLVVLAFLGILFVLWKLARLLRGK

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As discussed above, a S. pneumoniae AI sequence is present in the 19A Hungary 6 S. pneumoniae genome. Examples of S. pneumoniae AI sequences from 19A Hungary 6 are set forth below.

ORF2_19AH is a transcriptional regulator. An example of an amino acid sequence of

ORF2_19AH is set forth in SEQ ID NO: 187.

SEO ID NO: 187

MLNKYIEKRITDKITILNILLDIRSIELDELSTLTSLQSKSLLSILQELQETFEEELTFNLDTQQVQLIEHHSHQ
TNYYFHQLYNQSTILKILRFFLLQGNQSFNEFTQKEYISIATGYRVRQKCGLLLRSVGLDLVKNQVVGPEYRIRF
LIALLQFHFGIEIYDLNDGSMDWVTHMIVQSNSQLSHELLEITPDEYVHFSILVALTWKRREFPLEFPESKEFEK
LKNLFMYPILMEHCQTYLEPHANMTFTQEELDYIFLVYCSANSSFSKDKWNQEKKTHTIQLILQHTRGKHLLSKF
KNILGNDISNSLSFLTALTFLTRTFLFGLQNLVPYYNYYEHYGIESDKPLYHISKAIVQEWMTEQKIEGVIDQHR
LYLFSLYLTETIFSSLPAIPIFIILNNQADVNLIKSIILRNFTDKVASVTGYNILISPPPSEEHLTEPLIIITTK
EYLPYVKKQYPKGKHHFLTIALDLHVSQQRLIYQTIVDIRKEAFDKRVAMIAKKAHYLL

ORF3_19AH is a cell wall surface protein. An example of an amino acid sequence of

45 ORF3_19AH is set forth in SEQ ID NO: 188.

SEQ ID NO: 188

MKKVRKIFQKAVAGLCCISQLTAFSSIVALAETPETSPAIGKVVIKETGEGGALLGDAVFELKNNTDGTTVSQRT EAQTGEAIFSNIKPGTYTLTEAQPPVGYKPSTKQWTVEVEKNGRTTVQGEQVENREEALSDQYPQTGTYPDVQTP YQIIKVDGSEKNGQHKALNPNPYERVIPEGTLSKRIYQVNNLDDNQYGIELTVSGKTTVETKEASTPLDVVILLD NSNSMSNIRHNHAHRAEKAGEATRALVDKITSNPDNRVALVTYGSTIFDGSEATVEKGVADANGKILNDSALWTF DRTTFTAKTYNYSFLNLTSDPTDIQTIKDRIPSDAEELNKDKLMYQFGATFTQKALMTADDILTKQARPNSKKVIFHITDGVPTMSYPINFKYTGTTQSYRTQLNNFKAKTPNSSGILLEDFVTWSADGEHKIVRGDGESYQMFTKKPVT

DOYEVHOTESTSMEORAKEVSAGYRFYGTDLYLYWRDSILAYPFNSSTDWITNHGDPTTWYYNGNMAQDGYDVF TVGVGVNGDPGTDEATATRFMQSISSSPDNYTNVADPSQILQELNRYFYTIVNEKKSIENGTITDPMGELIDFQL GADGRFDPADYTLTANDGSSLVNNVPTGGPQNDGGLLKNAKVFYDTTEKRIRVTGLYLGTGEKVTLTYNVRLNDQ FVSNKFYDTNGRTTLHPKEVEKNTVRDFPIPKIRDVRKYPEITIPKEKKLGEIEFIKINKNDKKPLRDAVFSLQK QHPDYPDIYGAIDQNGTYQNVRTGEDGKLTFKNLSDGKYRLFENSEPAGYKPVQNKPIVAFQIVNGEVRDVTSIV PQDIPAGYEFTNDKHYITNEPIPPKREYPRTGGIGMLPFYLIGCMMMGGVLLYTRKNP

ORF4_19AH is a cell wall surface protein. An example of an amino acid sequence of ORF4_19AH is set forth in SEQ ID NO: 189.

10 SEO ID NO: 189

MKSINKFLTMLAALLLTASSLFSAATVFAADNVSTAPDAVTKTLTIHKLLLSEDDLKTWDTNGPKGYDGTQSSLK DLTGVVAEEIPNVYFELQKYNLTDGKEKENLKDDSKWTTVHGGLTTKDGLKIETSTLKGVYRIREDRTKTTYVGP NGQVLTGSKAVPALVTLPLVNNNGTVIDAHVFPKNSYNKPVVDKRIADTLNYNDQNGLSIGTKIPYVVNTTIPSN ATFATSFWSDEMTEGLTYNEDVTITLNNVAMDQADYEVTKGXNGFNLKLTEAGLAKINGKDADQKIQITYSATLN SLAVADIPESNDITYHYGNHQDHGNTPKPTKPNNGQITVTKTWDSQPAPEGVKATVQLVNAKTGEKVGAPVELSE NNWTYTWSGLDNSIEYKVEEEYNGYSAEYTVESKGKLGVKNWKDNNPAPINPEEPRVKTYGKKFVKVDQKDTRLE NAQFVVKKADSNKYIAFKSTAQQAADEKAAATAKQKLDAAVAAYTNAADKQAAQALVDQAQQEYNVAYKEAKFGY VEVAGKDEAMVLTSNTDGQFQISGLAAGTYKLEEIKAPEGFAKIDDVEFVVGAGSWNQGEFNYLKDVQKNDATKV VNKKITIPQTGGIGTIIFAVAGAAIMGIAVYAYVKNNKDEDOLA

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ORF5_19AH is a cell wall surface protein. An example of an amino acid sequence of ORF5_19AH is set forth in SEQ ID NO: 190.

SEQ ID NO: 190

MTMQKMQKMISRIFFVMALCFSLVWGAHAVQAQEDHTLVLQLENYQEVVSQLPSRDGHRLQVWKLDDSYSYDDRV QIVRDLHSWDENKLSSFKKTSFEMTFLENQIEVSHIPNGLYYVRSIIQTDAVSYPAEFLFEMTDQTVEPLVIVAK KTDTMTTKVKLIKVDQDHNRLEGVGFKLVSVARDGSEKEVPLIGEYRYSSSGQVGRTLYTDKNGEIFVTNLPLGN YRFKEVEPLAGYAVTTLDTDVQLVDHQLVTITVVNQKLPRGNVDFMKVDGRTNTSLQGAMFKVMKEESGHYTPVL QNGKEVVVTSGKDGRFRVEGLEYGTYYLWELQAPTGYVQLTSPVSFTIGKDTRKELVTVVKNNKRPRIDVPDTGE ETLYILMLVAILLFGSGYYLTKKPNN

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ORF6_19AH is a putative sortase. An example of an amino acid sequence of ORF6_19AH is set forth in SEQ ID NO: 191.

SEO ID NO: 191

MLIKMVKTKKQKRNNLLLGVVFFIGMAVMAYPLVSRLYYRVESNQQIADFDKEKATLDEADIDERMKLAQAFNDS LNNVVSGDPWSEEMKKKGRAEYARMLEIHERMGHVEIPVIDVDLPVYAGTAEEVLQQGAGHLEGTSLPIGGNSTH AVITAHTGLPTAKMFTDLTKLKVGDKFYVHNIKEVMAYQVDQVKVIEPTNFDDLLIVPGHDYVTLLTCTPYMINT HRLLVRGHRIPYVAEVEEEFIAANKLSHLYRYLFYVAVGLIVILLWIIRRLRKKKKQPEKALKALKAARKEVKVE DGQQ

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ORF7_19AH is a putative sortase. An example of an amino acid sequence of ORF7_19AH is set forth in SEQ ID NO: 192.

SEQ ID NO: 192

 $\label{thm:monskrskkgtkkkhplilliflugfavaiypluskyyriesnevikefdetusqmdkaeleerwrlaqaf natlkpseildpfteqekkkgvseyanmlkvherigyveipaidqeipmyvgtseeilqkgagllegaslpvgge nthtvvtahrglptaelfsqldkmkkgdvfylhvldqvlayqvdqiltvepndfepvliqhgedyatltctpym inshrllvrgkripytapiaernravrergqfwlwlllaalvmilvlsygvyrhrrivkglekqleehhvkg$

ORF8_19AH is a putative sortase. An example of an amino acid sequence of ORF8_19AH is set forth in SEQ ID NO: 193.

50 SEO ID NO: 193

MSKAKLQKLLGYLLMLVALVIPVYCFGQMVLQSLGQVKGHEIFSESVTADSYQEQLQRSLDYNQRLDSQNRIVDP FLAEGYEVNYQVSDDPDAVYGYLSIPSLEIMEPVYLGADYHHLAMGLAHVDGTPLPVEGKGIRSVIAGHRAEPSH VFFRHLDQLKVGDALYYDNGQEIVEYQMMDTEIILPSEWEKLESVSSKNIMTLITCDPIPTFNKRLLVNFERVAV YQKSDPQTAAVARVAFTKEGQSVSRVATSQWLYRGLVVLAFMGILFVLWKLARLLRGK

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As discussed above, a S. preumoniae AI sequence is present in the 6B Finland 12 S.

pneumoniae genome. Examples of S. pneumoniae AI sequences from 6B Finland 12 are set forth below.

ORF2_6BF is a transcriptional regulator. An example of an amino acid sequence of ORF2_6BF is set forth in SEQ ID NO: 194.

SEO ID NO: 194

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MLNKYIEKRITDKITILNILLDIRSIELDELSTLTSLQSKSLLSILQELQETFEEELTFNLDTQQVQLIEHHSHQ
TNYYFHQLYNQSTILKILRFFLLQGNQSFNEFTQKEYISIATGYRVRQKCGLLLRSVGLDLVKNQVVGPEYRIRF
LIALLQFHFGIEIYDLNDGSMDWVTHMIVQSNSQLSHELLEITPDEYVHFSILVALTWKRREFPLEFPESKEFEK
LKNLFMYPILMEHCQTYLEPHANMTFTQEELDYIFLVYCSANSSFSKDKWNQEKKTHTIQLILQHTRGKHLLSKF
KNILGNDISNSLSFLTALTFLTRTFLFGLQNLVPYYNYYEHYGIESDKPLYHISKAIVQEWMTEQKIEGVIDQHR
LYLFSLYLTETIFSSLPAIPIFIILNNQADVNLIKSIILRNFTDKVASVTGYNILISPPPSEEHLTEPLIIITTK
EYLPYVKKQYPKGKHHFLTIALDLHVSQQRLIYQTIVDIRKEAFDKRVAMIAKKAHYLL

ORF3_6BF is a cell wall surface protein. An example of an amino acid sequence of ORF3_6BF is set forth in SEQ ID NO: 195.

SEO ID NO: 195

MKKVRKIFQKAVAGLCCISQLTAFSSIVALAETPETSPAIGKVVIKETGEGGALLGDAVFELKNNTDGTTVSQRT
EAQTGEAIFSNIKPGTYTLTEAQPPVGYKPSTKQWTVEVEKNGRTTVQGEQVENREEALSDQYPQTGTYPDVQTP
YQIIKVDGSEKNGQHKALNPNPYERVIPEGTLSKRIYQVNNLDDNQYGIELTVSGKTTVETKEASTPLDVVILLD
NSNSMSNIRHNHAHRAEKAGEATRALVDKITSNPDNRVALVTYGSTIFDGSEATVEKGVADANGKILNDSALWTF
DRTTFTAKTYNYSFLNLTSDPTDIQTIKDRIPSDAEELNKDKLMYQFGATFTQKALMTADDILTKQARPNSKKVI
FHITDGVPTMSYPINFKYTGTTQSYRTQLNNFKAKTPNSSGILLEDFVTWSADGEHKIVRGDGESYQMFTKKPVT
DQYGVHQILSITSMEQRAKLVSAGYRFYGTDLYLYWRDSILAYPFNSSTDWITNHGDPTTWYYNGNMAQDGYDVF
TVGVGVNGDPGTDEATATRFMQSISSSPDNYTNVADPSQILQELNRYFYTIVNEKKSIENGTITDPMGELIDFQL
GADGRFDPADYTLTANDGSSLVNNVPTGGPQNDGGLLKNAKVFYDTTEKRIRVTGLYLGTGEKVTLTYNVRLNDQ
FVSNKFYDTNGRTTLHPKEVEKNTVRDFPIPKIRDVRKYPEITIPKEKKLGEIEFIKINKNDKKPLRDAVFSLQK
QHPDYPDIYGAIDQNGTYQNVRTGEDGKLTFKNLSDGKYRLFENSEPAGYKPVQNKPIVAFQIVNGEVRDVTSIV
PQDIPAGYEFTNDKHYITNEPIPPKREYPRTGGIGMLPFYLIGCMMMGGVLLYTRKHP

ORF4_6BF is a cell wall surface protein. An example of an amino acid sequence of ORF4_6BF is set forth in SEQ ID NO: 196.

SEQ ID NO: 196

MKSINKFLTMLAALLLTASSLFSAATVFAADNVSTAPDAVTKTLTIHKLLLSEDDLKTWDTNGPKGYDGTQSSLK
DLTGVVAEEIPNVYFELQKYNLTDGKEKENLKDDSKWTTVHGGLTTKDGLKIETSTLKGVYRIREDRTKTTYVGP
NGQVLTGSKAVPALVTLPLVNNNGTVIDAHVFPKNSYNKPVVDKRIADTLNYNDQNGLSIGTKIPYVVNTTIPSN
ATFATSFWSDEMTEGLTYNEDVTITLNNVAMDQADYEVTKGNNGFNLKLTEAGLAKINGKDADQKIQITYSATLN
SLAVADIPESNDITYHYGNHQDHGNTPKPTKPNNGQITVTKTWDSQPAPEGVKATVQLVNAKTGEKVGAPVELSE
NNWTYTWSGLDNSIEYKVEEEYNGYSAEYTVESKGKLGVKNWKDNNPAPINPEEPRVKTYGKKFVKVDQKDTRLE
NAQFVVKKADSNKYIAFKSTAQQAADEKAAATAKQKLDAAVAAYTNAADKQAAQALVDQAQQEYNVAYKEAKFGY
VEVAGKDEAMVLTSNTDGQFQISGLAAGTYKLEEIKAPEGFAKIDDVEFVVGAGSWNQGEFNYLKDVQKNDATKV
VNKKITIPQTGGIGTIIFAVAGAAIMGIAVYAYVKNNKDEDOLA

ORF5_6BF is a cell wall surface protein. An example of an amino acid sequence of

45 ORF5_6BF is set forth in SEQ ID NO: 197.

SEQ ID NO: 197

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MTMQKMQKMISRIFFVMALCFSLVWGAHAVQAQEDHTLVLQLENYQEVVSQLPSRDGHRLQVWKLDDSYSYDDRV QIVRDLHSWDENKLSSFKKTSFEMTFLENQIEVSHIPNGLYYVRSIIQTDAVSYPAEFLFEMTDQTVEPLVIVAK KTDTMTTKVKLIKVDQDHNRLEGVGFKLVSVARDGSEKEVPLIGEYRYSSSGQVGRTLYTDKNGEIFVTNLPLGN YRFKEVEPLAGYAVTTLDTDVQLVDHQLVTITVVNQKLPRGNVDFMKVDGRTNTSLQGAMFKVMKEESGHYTPVL QNGKEVVVTSGKDGRFRVEGLEYGTYYLWELQAPTGYVQLTSPVSFTIGKDTRKELVTVVKNNKRPRIDVPDTGE ETLYILMLVAILLFGSGYYLTKKPNN

FORF6_6BF is a putative sortase. An example of an amino acid sequence of ORF6_6BF is set forth in SEQ ID NO: 198.

SEQ ID NO: 198

MLIKMVKTKKQKRNNLLLGVVFFIGMAVMAYPLVSRLYYRVESNQQIADFDKEKATLDEADIDERMKLAQAFNDS

LNNVVSGDPWSEEMKKKGRAEYARMLEIHERMGHVEIPVIDVDLPVYAGTAEEVLQQGAGHLEGTSLPIGGNSTH
AVITAHTGLPTAKMFTDLTKLKVGDKFYVHNIKEVMAYQVDQVKVIEPTNFDDLLIVPGHDYVTLLTCTPYMINT
HRLLVRGHRIPYVAEVEEEFIAANKLSHLYRYLFYVAVGLIVILLWIIRRLRKKKKQPEKALKALKAARKEVKVE
DGQQ

ORF7_6BF is a putative sortase. An example of an amino acid sequence of ORF7_6BF is set forth in SEQ ID NO: 199.

SEO ID NO: 199

MDNSRRSRKKGTKKKKHPLILLIFLVGFAVAIYPLVSRYYYRIESNEVIKEFDETVSQMDKAELEERWRLAQAF NATLKPSEILDPFTEQEKKKGVSEYANMLKVHERIGYVEIPAIDQEIPMYVGTSEEILQKGAGLLEGASLPVGGE NTHTVVTAHRGLPTAELFSQLDKMKKGDVFYLHVLDQVLAYQVDQILTVEPNDFEPVLIQHGEDYATLLTCTPYM INSHRLLVRGKRIPYTAPIAERNRAVRERGQFWLWLLLAALVMILVLSYGVYRHRRIVKGLEKQLEEHHVKG

ORF8_6BF is a putative sortase. An example of an amino acid sequence of ORF8_6BF is set forth in SEQ ID NO: 200.

20 SEQ ID NO: 200

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MSKÄKLQKLLGYLLMLVALVIPVYCFGQMVLQSLGQVKGHEIFSESVTADSYQEQLQRSLDYNQRLDSQNRIVDP FLAEGYEVNYQVSDDPDAVYGYLSIPSLEIMEPVYLGADYHHLAMGLAHVDGTPLPVEGKGIRSVIAGHRAEPSH VFFRHLDQLKVGDALYYDNGQEIVEYQMMDTEIILPSEWEKLESVSSKNIMTLITCDPIPTFNKRLLVNFERVAV YQKSDPQTAAVARVAFTKEGQSVSRVATSQWLYRGLVVLAFLGILFVLWKLARLLRGK

As discussed above, a S. pneumoniae AI sequence is present in the 6B Spain 2 S. pneumoniae genome. Examples of S. pneumoniae AI sequences from 6B Spain 2 are set forth below.

ORF2_6BSP is a transcriptional regulator. An example of an amino acid sequence of ORF2_6BSP is set forth in SEQ ID NO: 201.

30 SEO ID NO: 201

MLNKYIEKRITDKITILNILLDIRSIELDELSTLTSLQSKSLLSILQELQETFEEELTFNLDTQQVQLIEHHSHQ
TNYYFHQLYNQSTILKILRFFLLQGNQSFNEFTQKEYISIATGYRVRQKCGLLLRSVGLDLVKNQVVGPEYRIRF
LIALLQFHFGIEIYDLNDGSMDWVTHMIVQSNSQLSHELLEITPDEYVHFSILVALTWKRREFPLEFPESKEFEK
LKNLFMYPILMEHCQTYLEPHANMTFTQEELDYIFLVYCSANSSFSKDKWNQEKKTHTIQLILQHTRGKHLISKF
KNILGNDISNSLSFLTALTFLTRTFLFGLQNLVPYYNYYEHYGIESDKPLYHISKAIVQEWMTEQKIEGVIDQHR
LYLFSLYLTETIFSSLPAIPIFIILNNQADVNLIKSIILRNFTDKVASVTGYNILISPPPSEEHLTEPLIIITTK
EYLPYVKKQYPKGKHHFLTIALDLHVSQQRLIYQTIVDIRKEAFDKRVAMIAKKAHYLL

ORF3_6BSP is a cell wall surface protein. An example of an amino acid sequence of ORF3 6BSP is set forth in SEO ID NO: 202.

SEQ ID NO: 202

MKKVRKIFQKAVAGLCCISQLTAFSSIVALAETPETSPAIGKVVIKETGEGGALLGDAVFELKNNTDGTTVSQRT EAQTGEAIFSNIKPGTYTLTEAQPPVGYKPSTKQWTVEVEKNGRTTVQGEQVENREEALSDQYPQTGTYPDVQTP YQIIKVDGSEKNGQHKALNPNPYERVIPEGTLSKRIYQVNNLDDNQYGIELTVSGKTTVETKEASTPLDVVILLD NSNSMSNIRHNHAHRAEKAGEATRALVDKITSNPDNRVALVTYGSTIFDGSEATVEKGVADANGKILNDSALWTF DRTTFTAKTYNYSFLNLTSDPTDIQTIKDRIPSDAEELNKDKLMYQFGATFTQKALMTADDILTKQARPNSKKVI FHITDGVPTMSYPINFKYTGTTQSYRTQLNNFKAKTPNSSGILLEDFVTWSADGEHKIVRGDGESYQMFTKKPVT DQYGVHQILSITSMEQRAKLVSAGYRFYGTDLYLYWRDSILAYPFNSSTDWITNHGDPTTWYYNGNMAQDGYDVF TVGVGVNGDPGTDEATATRFMQSISSSPDNYTNVADPSQILQELNRYFYTIVNEKKSIENGTITDPMGELIDFQL GADGRFDPADYTLTANDGSSLVNNVPTGGPQNDGGLLKNAKVFYDTTEKRIRVTGLYLGTGEKVTLTYNVRLNDQ FVSNKFYDTNGRTTLHPKEVEKNTVRDFPIPKIRDVRKYPEITIPKEKKLGEIEFIKINKNDKKPLRDAVFSLQK QHPDYPDIYGAIDQNGTYQNVRTGEDGKLTFKNLSDGKYRLFENSEPAGYKPVQNKPIVAFQIVNGEVRDVTSIV PQDIPAGYEFTNDKHYITNEPIPPKREYPRTGGIGMLPFYLIGCMMMGGVLLYTRKHP

ORF4_6BSP is a cell wall surface protein. An example of an amino acid sequence of ORF4_6BSP is set forth in SEQ ID NO: 203.

SEO ID NO: 203

MKSINKFLTMLAALLLTASSLFSAATVFAADNVSTAPDAVTKTLTIHKLLLSEDDLKTWDTNGPKGYDGTQSSLK

DLTGVVAEEIPNVYFELQKYNLTDGKEKENLKDDSKWTTVHGGLTTKDGLKIETSTLKGVYRIREDRTKTTYVGP
NGQVLTGSKAVPALVTLPLVNNNGTVIDAHVFPKNSYNKPVVDKRIADTLNYNDQNGLSIGTKIPYVVNTTIPSN
ATFATSFWSDEMTEGLTYNEDVTITLNNVAMDQADYEVTKGNNGFNLKLTEAGLAKINGKDADQKIQITYSATLN
SLAVADIPESNDITYHYGNHQDHGNTPKPTKPNNGQITVTKTWDSQPAPEGVKATVQLVNAKTGEKVGAPVELSE
NNWTYTWSGLDNSIEYKVEEEYNGYSAEYTVESKGKLGVKNWKDNNPAPINPEEPRVKTYGKKFVKVDQKDTRLE
NAQFVVKKADSNKYIAFKSTAQQAADEKAAATAKQKLDAAVAAYTNAADKQAAQALVDQAQQEYNVAYKEAKFGY
VEVAGKDEAMVLTSNTDGQFQISGLAAGTYKLEEIKAPEGFAKIDDVEFVVGAGSWNQGEFNYLKDVQKNDATKV
VNKKITIPQTGGIGTIIFAVAGAAIMGIAVYAYVKNNKDEDQLA

ORF5_6BSP is a cell wall surface protein. An example of an amino acid sequence of ORF5_6BSP is set forth in SEQ ID NO: 204.

SEO ID NO: 204

MTMQKMQKMISRIFFVMALCFSLVWGAHAVQAQEDHTLVLQLENYQEVVSQLPSRDGHRLQVWKLDDSYSYDDRV QIVRDLHSWDENKLSSFKKTSFEMTFLENQIEVSHIPNGLYYVRSIIQTDAVSYPAEFLFEMTDQTVEPLVIVAK KTDTMTTKVKLIKVDQDHNRLEGVGFKLVSVARDGSEKEVPLIGEYRYSSSGQVGRTLYTDKNGEIFVTNLPLGN YRFKEVEPLAGYAVTTLDTDVQLVDHQLVTITVVNQKLPRGNVDFMKVDGRTNTSLQGAMFKVMKEESGHYTPVL QNGKEVVVTSGKDGRFRVEGLEYGTYYLWELQAPTGYVQLTSPVSFTIGKDTRKELVTVVKNNKRPRIDVPDTGE ETLYILMLVAILLFGSGYYLTKKPNN

ORF6_6BSP is a putative sortase. An example of an amino acid sequence of ORF6_6BSP is set forth in SEO ID NO: 205.

SEO ID NO: 205

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MLIKMVKTKKQKRNNLLLGVVFFIGMAVMAYPLVSRLYYRVESNQQIADFDKEKATLDEADIDERMKLAQAFNDS LNNVVSGDPWSEEMKKKGRAEYARMLEIHERMGHVEIPVIDVDLPVYAGTAEEVLQQGAGHLEGTSLPIGGNSTH AVITAHTGLPTAKMFTDLTKLKVGDKFYVHNIKEVMAYQVDQVKVIEPTNFDDLLIVPGHDYVTLLTCTPYMINT HRLLVRGHRIPYVAEVEEEFIAANKLSHLYRYLFYVAVGLIVILLWIIRRLRKKKKQPEKALKALKAARKEVKVE DGQQ

ORF7_6BSP is a putative sortase. An example of an amino acid sequence of ORF7_6BSP is set forth in SEQ ID NO: 206.

35 SEQ ID NO: 206

MDNSRRSRKKGTKKKKHPLILLLIFLVGFAVAIYPLVSRYYYRIESNEVIKEFDETVSQMDKAELEERWRLAQAF NATLKPSEILDPFTEQEKKKGVSEYANMLKVHERIGYVEIPAIDQEIPMYVGTSEEILQKGAGLLEGASLPVGGE NTHTVVTAHRGLPTAELFSQLDKMKKGĎVFYLHVLDQVLAYQVDQILTVEPNDFEPVLIQHGEDYATLLTCTPYM INSHRLLVRGKRIPYTAPIAERNRAVRERGQFWLWLLLAALVMILVLSYGVYRHRRIVKGLEKQLEEHHVKG

ORF8_6BSP is a putative sortase. An example of an amino acid sequence of ORF8_6BSP is set forth in SEQ ID NO: 207.

SEO ID NO: 207

MSKAKLQKLLGYLLMLVALVIPVYCFGQMVLQSLGQVKGHEIFSESVTADSYQEQLQRSLDYNQRLDSQNRIVDP
45 FLAEGYEVNYQVSDDPDAVYGYLSIPSLEIMEPVYLGADYHHLAMGLAHVDGTPLPVEGKGIRSVIAGHRAEPSH
VFFRHLDQLKVGDALYYDNGQEIVEYQMMDTEIILPSEWEKLESVSSKNIMTLITCDPIPTFNKRLLVNFERVAV
YQKSDPQTAAVARVAFTKEGQSVSRVATSQWLYRGLVVLAFLGILFVLWKLARLLRGK

As discussed above, a S. pneumoniae AI sequence is present in the 9V Spain 3 S. pneumoniae genome. Examples of S. pneumoniae AI sequences from 9V Spain 3 are set forth below.

ORF2_9VSP is a transcriptional regulator. An example of an amino acid sequence of ORF2_9VSP is set forth in SEQ ID NO: 208.

SEQ.D NO. 208 U 5 / 2 7 2 3 4

MLNKYIEKRITDKITILNILLDIRSIELDELSTLTSLQSKSLLSILQELQETFEEELTFNLDTQQVQLIEHHSHQ
TNYYFHQLYNQSTILKILRFFLLQGNQSFNEFTQKEYISIATGYRVRQKCGLLLRSVGLDLVKNQVVGPEYRIRF
LIALLQFHFGIEIYDLNDGSMDWVTHMIVQSNSQLSHELLEITPDEYVHFSILVALTWKRREFPLEFPESKEFEK
LKNLFMYPILMEHCQTYLEPHANMTFTQEELDYIFLVYCSANSSFSKDKWNQEKKTHTIQLILQHTRGKHLLSKF
KNILGNDISNSLSFLTALTFLTRTFLFGLQNLVPYYNYYEHYGIESDKPLYHISKAIVQEWMTEQKIEGVIDQHR
LYLFSLYLTETIFSSLPAIPIFIILNNQADVNLIKSIILRNFTDKVASVTGYNILISPPPSEEHLTEPLIIITTK
EYLPYVKKQYPKGKHHFLTIALDLHVSQQRLIYQTIVDIRKEAFDKRVAMIAKKAHYLL

ORF3_9VSP is a cell wall surface protein. An example of an amino acid sequence of ORF3_9VSP is set forth in SEQ ID NO: 209.

SEQ ID NO: 209

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MKKVRKIFQKAVAGLCCISQLTAFSSIVALAETPETSPAIGKVVIKETGEGGALLGDAVFELKNNTNGTTVSQRT
EAQTGEAIFSNIKPGTYTLTEAQPPVGYKPSTKQRTVEVEKNGRTTVQGEQVENREEALSDQYPQTGTYPDVQTP
YQIIKVDGSEKNGQHKALNPNPYERVIPEGTLSKRIYQVNNLDDNQYGIELTVSGKTVYERKDKSVPLDVVILLD
NSNSMSNIRNKNARRAERAGEATRSLIDKITSDPENRVALVTYASTIFDGTEFTVEKGVADKNGKRLNDSLFWNY
DQTSFTTNTKDYSYLKLTNDKNDIVELKNKVPTEAEDHDGNRLMYQFGATFTQKALMKADEILTQQARQNSQKVI
FHITDGVPTMSYPINFNHATFAPSYQNQLNAFFSKSPNKDGILLSDFITQATSGEHTIVRGDGQSYQMFTDKTVY
EKGAPAAFPVKPEKYSEMKAVGYAVIGDPINGGYIWLNWRESILAYPFNSNTAKITNHGDPTRWYYNGNIAPDGY
DVFTVGIGINGDPGTDEATATSFMQSISSKPENYTNVTDTTKILEQLNRYFHTIVTEKKSIENGTITDPMGELID
LQLGTDGRFDPADYTLTANDGSRLENGQAVGGPQNDGGLLKNAKVFYDTTEKRIRVTGLYLGTGEKVTLTYNVRL
NDQFVSNKFYDTNGRTTLHPKEVEKNTVRDFPIPKIRDVRKYPAITIAKEKKLGEIEFIKINKNDKKPLRDAVFS
LQKQHPDYPDIYGAIDQNGTYQNVRTGEDGKLTFKNLSDGKYRLFENSEPAGYKPVQNKPIVAFQIVNGEVRDVT
SIVPQDIPAGYEFTNDKHYITNEPIPPKREYPRTGGIGMLLFYLIGCMMMGGVLLYTRKHP

ORF4_9VSP is a cell wall surface protein. An example of an amino acid sequence of ORF4_9VSP is set forth in SEQ ID NO: 210.

SEQ ID NO: 210

MKSINKFLTMLAALLLTASSLFSAATVFAAGTTTTSVTVHKLLATDGDMDKIANELETGNYAGNKVGVLPANAKE
IAGVMFVWTNTNNEIIDENGQTLGVNIDPQTFKLSGAMPATAMKKLTEAEGAKFNTANLPAAKYKIYEIHSLSTY
VGEDGATLTGSKAVPIEIELPLNDVVDAHVYPKNTEAKPKIDKDFKGKANPDTPRVDKDTPVNHQVGDVVEYEIV
TKIPALANYATANWSDRMTEGLAFNKGTVKVTVDDVALEAGDYALTEVATGFDLKLTDAGLAKVNDQNAEKTVKI
TYSATLNDKAIVEVPESNDVTFNYGNNPDHGNTPKPNKPNENGDLTLTKTWVDATGAPIPAGAEATFDLVNAQTG
KVVQTVTLTTDKNTVTVNGLDKNTEYKFVERSIKGYSADYQEITTAGEIAVKNWKDENPKPLDPTEPKVVTYGKK
FVKVNDKDNRLAGAEFVIANADNAGQYLARKADKVSQEEKQLVVTTKDALDRAVAAYNALTAQQQTQQEKEKVDK
AQAAYNAAVIAANNAFEWVADKDNENVVKLVSDAQGRFEITGLLAGTYYLEETKQPAGYALLTSRQKFEVTATSY
SATGQGIEYTAGSGKDDATKVVNKKITIPQTGGIGTIIFAVAGAVIMGIAVYAYVKNNKDEDQLA

ORF5_9VSP is a cell wall surface protein. An example of an amino acid sequence of ORF5_9VSP is set forth in SEQ ID NO: 211.

SEO ID NO: 211

MTMQKMQKMQKMQKMQKMISRIFFVMALCFSLVWGAHAVQAQEDHTLVLQLENYQEVVSQLPSRDGHRLQVW KLDDSYSYDNRVQIVRDLHSWDENKLSSFKKTSFEMTFLENQIEVSHIPNGLYYVRSIIQTDAVSYPAEFLFEMT DQTVEPLVIVAKKADTVTTKVKLIKVDQDHNRLEGVGFKLVSVARDGSEKEVPLIGEYRYSSSGQVGRTLYTDKN GEIVVTNLPLGTYRFKEVEPLAGYTVTTMDTDVQLVDHQLVTITVVNQKLPRGNVDFMKVDGRTNTSLQGAMFKV MKEENGHYTPVLQNGKEVVVASGKDGRFRVEGLEYGTYYLWELQAPTGYVQLTSPVSFTIGKDTRKELVTVVKNN KRPRIDVPDTGEETLYILMLVAILLFGSGYYLTKKTNN

ORF6_9VSP is a putative sortase. An example of an amino acid sequence of ORF6_9VSP is set forth in SEQ ID NO: 212.

SEQ ID NO: 212

MLIKMAKTKKQKRNNLLLGVVFFIGIAVMAYPLVSRLYYRVESNQQIADFDKEKATLDEADIDERMKLAQAFNDS LNNVVSGDPWSEEMKKKGRAEYARMLEIHERMGHVEIPAIDVDLPVYAGTAEEVLQQGAGHLEGTSLPIGGNSTH AVITAHTGLPTAKMFTDLTKLKVGDKFYVHNIKEVMAYQVDQVKVIEPTNFDDLLIVPGHDYVTLLTCTPYMINT HRLLVRGHRIPYVAEVEEEFIAANKLSHLYRYLFYVAVGLIVILLWIIRRLRKKKRQSERALKALKEATKEVKVE

ORF7_9VSP is a putative sortase. An example of an amino acid sequence of ORF7_9VSP is set forth in SEQ ID NO: 213.

SEQ ID NO: 213

MSKSRYSRKKSVKKKKNPFILLLIFLVGLAVAMYPLVSRYYYRIESNEVIKEFDETVSQMDKAELEERWRLAQAF NATLKPSEILDPFTEQEKKKGVSEYANMLKVHERIGYVEIPAIDQEIPMYVGTSEEILQKGAGLLEGASLPVGGE NTHTVVTAHRGLPTAELFSQLDKMKKGDIFYLHVLDQVLAYQVDQIVTVEPNDFEPVLIQHGEDYATLLTCTPYM INSHRLLVRGKRIPYTAPIAERNRAVRERGQFWLWLLLGAMAVILLLLYRVYRNRRIVKGLEKQLEGRHVKD

ORF8_9VSP is a putative sortase. An example of an amino acid sequence of ORF8_9VSP is set forth in SEQ ID NO: 214.

SEO ID NO: 214

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MSRTKLRALLGYLLMLVACLIPIYCFGQMVLQSLGQVKGHATFVKSMTTEMYQEQQNHSLAYNQRLASQNRIVDP FLAEGYEVNYQVSDDPDAVYGYLSIPSLEIMEPVYLGADYHHLGMGLAHVDGTPLPLDGTGIRSVIAGHRAEPSH VFFRHLDQLKVGDALYYDNGQEIVEYQMMDTEIILPSEWEKLESVSSKNIMTLITCDPIPTFNKRLLVNFERVAV YQKSDPQTAAVARVAFTKEGQSVSRVATSQWLYRGLVVLAFLGILFVLWKLARLLRGK

As discussed above, a S. pneumoniae AI sequence is present in the 14 CSR 10 S. pneumoniae genome. Examples of S. pneumoniae AI sequences from 14 CSR 10 are set forth below.

ORF2_14CSR is a transcriptional regulator. An example of an amino acid sequence of ORF2_14CSR is set forth in SEQ ID NO: 215.

SEQ ID NO: 215

MLNKYIEKRITDKITILNILLDIRSIELDELSTLTSLQSKSLLSILQELQETFEEELTFNLDTQQVQLIEHHSHQ
TNYYFHQLYNQSTILKILRFFLLQGNQSFNEFTQKEYISIATGYRVRQKCGLLLRSVGLDLVKNQVVGPEYRIRF
LIALLQFHFGIEIYDLNDGSMDWVTHMIVQSNSQLSHELLEITPDEYVHFSILVALTWKRREFPLEFPESKEFEK
LKNLFMYPILMEHCQTYLEPHANMTFTQEELDYIFLVYCSANSSFSKDKWNQEKKTHTIQLILQHTRGKHLLSKF
KNILGNDISNSLSFLTALTFLTRTFLFGLQNLVPYYNYYEHYGIESDKPLYHISKAIVQEWMTEQKIEGVIDQHR
LYLFSLYLTETIFSSLPAIPIFIILNNQADVNLIKSIILRNFTDKVASVTGYNILISPPPSEEHLTEPLIIITTK
EYLPYVKKQYPKGKHHFLTIALDLHVSQQRLIYQTIVDIRKEAFDKRVAMIAKKAHYLL

ORF3_14CSR is a cell wall surface protein. An example of an amino acid sequence of ORF3_14CSR is set forth in SEQ ID NO: 216.

SEQ ID NO: 216

MKKVRKIFQKAVAGLCCISQLTAFSSIVALAETPETSPAIGKVVIKETGEGGALLGDAVFELKNNTDGTTVSQRT
EAQTGEAIFSNIKPGTYTLTEAQPPVGYKPSTKQWTVEVEKNGRTTVQGEQVENREEALSDQYPQTGTYPDVQTP
YQIIKVDGSEKNGQHKALNPNPYERVIPEGTLSKRIYQVNNLDDNQYGIELTVSGKTTVETKEASTPLDVVILLD
NSNSMSNIRHNHAHRAEKAGEATRALVDKITSNPDNRVALVTYGSTIFDGSEATVEKGVADANGKILNDSALWTF
DRTTFTAKTYNYSFLNLTSDPTDIQTIKDRIPSDAEELNKDKLMYQFGATFTQKALMTADDILTKQARPNSKKVI
FHITDGVPTMSYPINFKYTGTTQSYRTQLNNFKAKTPNSSGILLEDFVTWSADGEHKIVRGDGESYQMFTKKPVT
DQYGVHQILSITSMEQRAKLVSAGYRFYGTDLYLYWRDSILAYPFNSSTDWITNHGDPTTWYYNGNMAQDGYDVF
TVGVGVNGDPGTDEATATRFMQSISSSPDNYTNVADPSQILQELNRYFYTIVNEKKSIENGTITDPMGELIDFQL
GADGRFDPADYTLTANDGSSLVNNVPTGGPQNDGGLLKNAKVFYDTTEKRIRVTGLYLGTGEKVTLTYNVRLNDQ
FVSNKFYDTNGRTTLHPKEVEKNTVRDFPIPKIRDVRKYPEITIPKEKKLGEIEFIKINKNDKKPLRDAVFSLQK
QHPDYPDIYGAIDQNGTYQNVRTGEDGKLTFKNLSDGKYRLFENSEPAGYKPVQNKPIVAFQIVNGEVRDVTSIV
PQDIPAGYEFTNDKHYITNEPIPPKREYPRTGGIGMLPFYLIGCMMMGGVLLYTRKHP

ORF4_14CSR is a cell wall surface protein. An example of an amino acid sequence of ORF4_14CSR is set forth in SEQ ID NO: 217.

SEO ID NO: 217

MKSINKFLTMLAALLLTASSLFSAATVFAADNVSTAPDAVTKTLTIHKLLLSEDDLKTWDTNGPKGYDGTQSSLK DLTGVVAEEIPNVYFELQKYNLTDGKEKENLKDDSKWTTVHGGLTTKDGLKIETSTLKGVYRIREDRTKTTYVGP NGQVLTGSKAVPALVTLPLVNNNGTVIDAHVFPKNSYNKPVVDKRIADTLNYNDQNGLSIGTKIPYVVNTTIPSN ATFATSFWSDEMTEGLTYNEDVTITLNNVAMDQADYEVTKGNNGFNLKLTEAGLAKINGKDADQKIQITYSATLN SLAVADIPESNDITYHYGNHQDHGNTPKPTKPNNGQITVTKTWDSQPAPEGVKATVQLVNAKTGEKVGAPVELSE

NAMEYTWSGLOWSTELKVEERVOYGAEYTVESKGKLGVKNWKDNNPAPINPEEPRVKTYGKKFVKVDQKDTRLE NAQFVVKKADSNKYIAFKSTAQQAADEKAAATAKQKLDAAVAAYTNAADKQAAQALVDQAQQEYNVAYKEAKFGY VEVAGKDEAMVLTSNTDGQFQISGLAAGTYKLEEIKAPEGFAKIDDVEFVVGAGSWNQGEFNYLKDVQKNDATKV VNKKITIPQTGGIGTIIFAVAGAAIMGIAVYAYVKNNKDEDOLA

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ORF5_14CSR is a cell wall surface protein. An example of an amino acid sequence of ORF5_14CSR is set forth in SEQ ID NO: 218.

SEQ ID NO: 218

MTMQKMQKMISRIFFVMALCFSLVWGAHAVQAQEDHTLVLQLENYQEVVSQLPSRDGHRLQVWKLDDSYSYDDRV
QIVRDLHSWDENKLSSFKKTSFEMTFLENQIEVSHIPNGLYYVRSIIQTDAVSYPAEFLFEMTDQTVEPLVIVAK
KTDTMTTKVKLIKVDQDHNRLEGVGFKLVSVARDGSEKEVPLIGEYRYSSSGQVGRTLYTDKNGEIFVTNLPLGN
YRFKEVEPLAGYAVTTLDTDVQLVDHQLVTITVVNQKLPRGNVDFMKVDGRTNTSLQGAMFKVMKEESGHYTPVL
QNGKEVVVTSGKDGRFRVEGLEYGTYYLWELQAPTGYVQLTSPVSFTIGKDTRKELVTVVKNNKRPRIDVPDTGE
ETLYILMLVAILLFGSGYYLTKKPNN

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ORF6_14CSR is a putative sortase. An example of an amino acid sequence of ORF6_14CSR is set forth in SEQ ID NO: 219.

SEQ ID NO: 219

MLIKMVKTKKQKRNNLLLGVVFFIGMAVMAYPLVSRLYYRVESNQQIADFDKEKATLDEADIDERMKLAQAFNDS
LNNVVSGDPWSEEMKKKGRAEYARMLEIHERMGHVEIPVIDVDLPVYAGTAEEVLQQGAGHLEGTSLPIGGNSTH
AVITAHTGLPTAKMFTDLTKLKVGDKFYVHNIKEVMAYQVDQVKVIEPTNFDDLLIVPGHDYVTLLTCTPYMINT
HRLLVRGHRIPYVAEVEEEFIAANKLSHLYRYLFYVAVGLIVILLWIIRRLRKKKKQPEKALKALKAARKEVKVE
DGQQ

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ORF7_14CSR is a putative sortase. An example of an amino acid sequence of ORF7_14CSR is set forth in SEQ ID NO: 220.

SEQ ID NO: 220

 $\label{thm:monsrskkgtkkkhplilliflvgfavaiyplvsryyriesnevikefdetvsqmdkaeleerwrlaqaf natlkpseildpfteqekkkgvseyanmlkvherigyveipaidqeipmyvgtseeilqkgagllegaslpvgge nthtvvtahrglptaelfsqldkmkkgdvfylhvldqvlayqvdqiltvepndfepvliqhgedyatltctpym inshrllvrgkripytapiaernravrergqfwlwlllaalvmilvlsygvyrhrrivkglekqleehhvkg$

ORF8_14CSR is a putative sortase. An example of an amino acid sequence of ORF8_14CSR is set forth in SEQ ID NO: 221.

35 SEQ ID NO: 221

MSKAKLQKLLGYLLMLVALVIPVYCFGQMVLQSLGQVKGHEIFSESVTADSYQEQLQRSLDYNQRLDSQNRIVDP FLAEGYEVNYQVSDDPDAVYGYLSIPSLEIMEPVYLGADYHHLAMGLAHVDGTPLPVEGKGIRSVIAGHRAEPSH VFFRHLDQLKVGDALYYDNGQEIVEYQMMDTEIILPSEWEKLESVSSKNIMTLITCDPIPTFNKRLLVNFERVAV YQKSDPQTAAVARVAFTKEGQSVSRVATSQWLYRGLVVLAFLGILFVLWKLARLLRGK

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As discussed above, a S. pneumoniae AI sequence is present in the 19F Taiwan 14 S. pneumoniae genome. Examples of S. pneumoniae AI sequences from 19F Taiwan 14 are set forth below.

ORF2_19FTW is a transcriptional regulator. An example of an amino acid sequence of ORF2_19FTW is set forth in SEO ID NO: 222.

SEO ID NO: 222

MLNKYIEKRITDKITILNILLDIRSIELDELSTLTSLQSKSLLSILQELQETFEELTFNLDTQQVQLIEHHSHQ
TNYYFHQLYNQSTILKILRFFLLQGNQSFNEFTQKEYISIATGYRVRQKCGLLLRSVGLDLVKNQVVGPEYRIRF
LIALLQFHFGIEIYDLNDGSMDWVTHMIVQSNSQLSHELLEITPDEYVHFSILVALTWKRREFPLEFPESKEFEK
LKNLFMYPILMEHCQTYLEPHANMTFTQEELDYIFLVYCSANSSFSKDKWNQEKKTHTIQLILQHTRGKHLLSKF
KNILGNDISNSLSFLTALTFLTRTFLFGLQNLVPYYNYYEHYGIESDKPLYHISKAIVQEWMTEQKIEGVIDQHR
LYLFSLYLTETIFSSLPAIPIFIILNNQADVNLIKSIILRNFTDKVASVTGYNILISPPPSEEHLTEPLIIITTK
EYLPYVKKQYPKGKHHFLTIALDLHVSQQRLIYQTIVDIRKEAFDKRVAMIAKKAHYLL

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ORF3_19FTW is a cell wall surface protein. An example of an amino acid sequence of ORF3_19FTW is set forth in SEQ ID NO: 223.

SEQ ID NO: 223

5 MKKVRKIFQKAVAGLCCISQLTAFSSIVALAETPETSPAIGKVVIKETGEGGALLGDAVFELKNNTDGTTVSQRT
EAQTGEAIFSNIKPGTYTLTEAQPPVGYKPSTKQWTVEVEKNGRTTVQGEQVENREEALSDQYPQTGTYPDVQTP
YQIIKVDGSEKNGQHKALNPNPYERVIPEGTLSKRIYQVNNLDDNQYGIELTVSGKTVYERKDKSVPLDVVILLD
NSNSMSNIRNKNARRAERAGEATRSLIDKITSDPENRVALVTYASTIFDGTEFTVEKGVADKNGKRLNDSLFWNY
DQTSFTTNTKDYSYLKLTNDKNDIVELKNKVPTEAEDHDGNRLMYQFGATFTQKALMKADEILTQQARQNSQKVI
FHITDGVPTMSYPINFNHATFAPSYQNQLNAFFSKSPNKDGILLSDFITQATSGEHTIVRGDGQSYQMFTDKTVY
EKGAPAAFPVKPEKYSEMKAVGYAVIGDPINGGYIWLNWRESILAYPFNSNTAKITNHGAPTRWYYNGNIAPDGY
DVFTVGIGINGDPGTDEATATSFMQSISSKPENYTNVTDTTKILEQLNRYFHTIVTEKKSIENGTITDPMGELID
LQLGTDGRFDPADYTLTANDGSRLENGQAVGGPQNDGGLLKNAKVFYDTTEKRIRVTGLYLGTGEKVTLTYNVRL
NDQFVSNKFYDTNGRTTLHPKEVEKNTVRDFPIPKIRDVRKYPAITIAKEKKLGEIEFIKINKNDKKPLRDAVFS
LQKQHPDYPDIYGAIDQNGTYQNVRTGEDGKLTFKNLSDGKYRLFENSEPAGYKPVQNKPIVAFQIVNGEVRDVT
SIVPQDIPAGYEFTNDKHYITNEPIPPKREYPRTGGIGMLPFYLIGCMMMGGVLLYTRKHP

ORF4_19FTW is a cell wall surface protein. An example of an amino acid sequence of ORF4_19FTW is set forth in SEQ ID NO: 224.

20 SEQ ID NO: 224

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MKSINKFLTMLAALLLTASSLFSAATVFAAGTTTTSVTVHKLLATDGDMDKIANELETGNYAGNKVGVLPANAKE IAGVMFVWTNTNNEIIDENGQTLGVNIDPQTFKLSGAMPATAMKKLTEAEGAKFNTANLPAAKYKIYEIHSLSTY VGEDGATLTGSKAVPIEIELPLNDVVDAHVYPKNTEAKPKIDKDFKGKANPDTPRVDKDTPVNHQVGDVVEYEIV TKIPALANYATANWSDRMTEGLAFNKGTVKVTVDDVALEAGDYALTEVATGFDLKLTDAGLAKVNDQNAEKTVKI TYSATLNDKAIVEVPESNDVTFNYGNNPDHGNTPKPNKPNENGDLTLTKTWVDATGAPIPAGAEATFDLVNAQTG KVVQTVTLTTDKNTVTVNGLDKNTEYKFVERSIKGYSADYQEITTAGEIAVKNWKDENPKPLDPTEPKVVTYGKK FVKVNDKDNRLAGAEFVIANADNAGQYLARKADKVSQEEKQLVVTTKDALDRAVAAYNALTAQQQTQQEKEKVDK AQAAYNAAVIAANNAFEWVADKDNENVVKLVSDAQGRFEITGLLAGTYYLEETKQPAGYALLTSRQKFEVTATSY SATGQGIEYTAGSGKDDATKVVNKKITIPQTGGIGTIIFAVAGAVIMGIAVYAYVKNNKDEDQLA

ORF5_19FTW is a cell wall surface protein. An example of an amino acid sequence of ORF5_19FTW is set forth in SEQ ID NO: 225.

SEO ID NO: 225

MTMQKMQKMISRIFFVMALCFSLVWGAHAVQAQEDHTLVLQLENYQEVVSQLPSRDGHRLQVWKLDDSYSYDNRV QIVRDLHSWDENKLSSFKKTSFEMTFLENQIEVSHIPNGLYYVRSIIQTDAVSYPAEFLFEMTDQTVEPLVIVAK KADTVTTKVKLIKVDQDHNRLEGVGFKLVSVARDGSEKEVPLIGEYRYSSSGQVGRTLYTDKNGEIVVTNLPLGT YRFKEVEPLAGYTVTTMDTDVQLVDHQLVTITVVNQKLPRGNVDFMKVDGRTNTSLQGAMFKVMKEENGHYTPVL QNGKEVVVASGKDGRFRVEGLEYGTYYLWELQAPTGYVQLTSPVSFTIGKDTRKELVTVVKNNKRPRIDVPDTGE ETLYILMLVAILLFGSGYYLTKKTNN

ORF6_19FTW is a putative sortase. An example of an amino acid sequence of ORF6_19FTW is set forth in SEQ ID NO: 226.

SEO ID NO: 226

MLIKMAKTKKQKRNNLLLGVVFFIGMAVMAYPLVSRLYYRVESNQQIADFDKEKATLDEADIDERMKLAQAFNDS LNNVVSGDPWSEEMKKKGRAEYARMLEIHERMGHVEIPAIDVDLPVYAGTAEEVLQQGAGHLEGTSLPIGGNSTH AVITAHTGLPTAKMFTDLTKLKVGDKFYVHNIKEVMAYQVDQVKVIEPTNFDDLLIVPGHDYVTLLTCTPYMINT HRLLVRGHRIPYVAEVEEEFIAANKLSHLYRYLFYVAVGLIVILLWIIRRLRKKKRQSERALKALKEATKEVKVE DE

ORF7_19FTW is a putative sortase. An example of an amino acid sequence of ORF7_19FTW is set forth in SEQ ID NO: 227.

SEO ID NO: 227

MSKSRYSRKKSVKKKKNPFILLLIFLVGLAVAMYPLVSRYYYRIESNEVIKEFDETVSQMDKAELEERWRLAQAF NATLKPSEILDPFTDOEKKQGVSEYANMLKVHERIGYVEIPAIEOEIPMYVGTSEDILOKGAGLLEGASLPVGGE

NFHCVITAHROLETAELISQUEKNKKGGIFTLHVLDQVLAYQVDQIVTVEPNDFEPVLIQHGQDYATLLTCTPYM INSHRLLVRGKRIPYTAPIAERNRAVRERGQFWLWLLLGAMAVILLLLYRVYRNRRIVKGLEKQLEGRHVKD

ORF8 19FTW is a putative sortase. An example of an amino acid sequence of

5 ORF8 19FTW is set forth in SEQ ID NO: 228.

SEQ ID NO: 228

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MSRTKLRALLGYLLMLVACLIPIYCFGQMVLQSLGQVKGHATFVKSMTTEMYQEQQNHSLAYNQRLASQNRIVDP FLAEGYEVNYQVSDDPDAYYGYLSIPSLEIMEPVYLGADYHHLGMGLAHVDGTPLPLDGTGIRSVIAGHRAEPSH VFFRHLDQLKVGDALYYDNGQEIVEYQMMDTEIILPSEWEKLESVSSKNIMTLITCDPIPTFNKRLLVNFERVAV YQKSDPQTAAVARVAFTKEGQSVSRVATSQWLYRGLVVLAFLGILFVLWKLARLLRGK

As discussed above, a *S. pneumoniae* AI sequence is present in the 23F Taiwan 15 *S. pneumoniae* genome. Examples of *S. pneumoniae* AI sequences from 23F Taiwan 15 are set forth below.

ORF2_23FTW is a transcriptional regulator. An example of an amino acid sequence of ORF2_23FTW is set forth in SEQ ID NO: 229.

SEQ ID NO: 229

MLNKYIEKRITDKITILNILLDIRSIELDELSTLTSLQSKSLLSILQELQETFEEELTFNLDTQQVQLIEHHSHQ
TNYYFHQLYNQSTILKILRFFLLQGNQSFNEFTQKEYISIATGYRVRQKCGLLLRSVGLDLVKNQVVGPEYRIRF
LIALLQFHFGIEIYDLNDGSMDWVTHMIVQSNSQLSHELLEITPDEYVHFSILVALTWKRREFPLEFPESKEFEK
LKNLFMYPILMEHCQTYLEPHANMTFTQEELDYIFLVYCSANSSFSKDKWNQEKKTHTIQLILQHTRGKHLLSKF
KNILGNDISNSLSFLTALTFLTRTFLFGLQNLVPYYNYYEHYGIESDKPLYHISKAIVQEWMTEQKIEGVIDQHR
LYLFSLYLTETIFSSLPAIPIFIILNNQADVNLIKSIILRNFTDKVASVTGYNILISPPPSEEHLTEPLIIITTK
EYLPYVKKQYPKGKHHFLTIALDLHVSQQRLIYQTIVDIRKEAFDKRVAMIAKKAHYLL

ORF3_23FTW is a cell wall surface protein. An example of an amino acid sequence of ORF3_23FTW is set forth in SEQ ID NO: 230.

SEO ID NO: 230

MKKVRKIFQKAVAGLCCISQLTAFSSIVALAETPETSPAIGKVVIKETGEGGALLGDAVFELKNNTDGTTVSQRT EAQTGEAIFSNIKPGTYTLTEAQPPVGYKPSTKQWTVEVEKNGRTTVQGEQVENREEALSDQYPQTGTYPDVQTP YQIIKVDGSEKNGQHKALNPNPYERVIPEGTLSKRIYQVNNLDDNQYGIELTVSGKTVYEQKDKSVPLDVVILLD NSNSMSNIRNKNARRAERAGEATRSLIDKITSDPENRVALVTYASTIFDGTEFTVEKGVADKNGKRLNDSLFWNY DQTSFTTNTKDYSYLKLTNDKNDIVELKNKVPTEAEDHDGNRLMYQFGATFTQKALMKADEILTQQARQNSQKVI FHITDGVPTMSYPINFNHATFAPSYQNQLNAFFSKSPNKDGILLSDFITQATSGEHTIVRGDGQSYQMFTDKTVY EKGAPAAFPVKPEKYSEMKAAGYAVIGDPINGGYIWLNWRESILAYPFNSNTAKITNHGDPTRWYYNGNIAPDGY DVFTVGIGINGDPGTDEATATSFMQSISSKPENYTNVTDTTKILEQLNRYFHTIVTEKKSIENGTITDPMGELID LQLGTDGRFDPADYTLTANDGSRLENGQAVGGPQNDGGLLKNAKVLYDTTEKRIRVTGLYLGTDEKVTLTYNVRL NDEFVSNKFYDTNGRTTLHPKEVEQNTVRDFPIPKIRDVRKYPEITISKEKKLGDIEFIKVNKNDKKPLRDAVFS LQKQHPDYPDIYGAIDQNGTYQNVRTGEDGKLTFKNLSDGKYRLFENSEPAGYKPVQNKPIVAFQIVNGEVRDVT SIVPQDIPAGYEFTNDKHYITNEPIPPKREYPRTGGIGMLPFYLIGCMMMGGVLLYTRKHP

ORF4_23FTW is a cell wall surface protein. An example of an amino acid sequence of ORF4_23FTW is set forth in SEQ ID NO: 231.

SEQ ID NO: 231

45 MKSINKFLTILAALLLTVSSLFSAATVFAAEQKTKTLTVHKLLMTDQELDAWNSDAITTAGYDGSQNFEQFKQLQ
GVPQGVTEISGVAFELQSYTGPQGKEQENLTNDAVWTAVNKGVTTETGVKFDTEVLQGTYRLVEVRKESTYVGPN
GKVLTGMKAVPALITLPLVNQNGVVENAHVYPKNSEDKPTATKTFDTAAGFVDPGEKGLAIGTKVPYIVTTTIPK
NSTLATAFWSDEMTEGLDYNGDVVVNYNGQPLDNSHYTLEAGHNGFILKLNEKGLEAINGKDAEATITLKYTATL
NALAVADVPEANDVTFHYGNNPGHGNTPKPNKPKNGELTITKTWADAKDAPIAGVEVTFDLVNAQTGEVVKVPGH
ETGIVLNQTNNWTFTATGLDNNTEYKFVERTIKGYSADYQTITETGKIAVKNWKDENPEPINPEEPRVKTYGKKF
VKVDQKDERLKEAQFVVKNEQGKYLALKSAAQQAVNEKAAAEAKQALDAAIAAYTNAADKNAAQAVVDAAQKTYN
DNYRAARFGYVEVERKEDALVLTSNTDGQFQISGLAAGSYTLEETKAPEGFAKLGDVKFEVGAGSWNQGDFNYLK
DVQKNDATKVVNKKITIPQTGGIGTIIFAVAGAVIMGIAVYAYVKNNKDEDQLA

ORF5_23FTW is a cell will surface protein. An example of an amino acid sequence of ORF5_23FTW is set forth in SEQ ID NO: 232.

SEO ID NO: 232

MTMQKMQKMISRIFFVMALCFSLVWGAHAVQAQEDHTLVLQLENYQEVVSQLPSRDGHRLQVWKLDDSYSYDNRV QIVRDLHSWDENKLSSFKKTSFEMTFLENQIEVSHIPNGLYYVRSIIQTDAVSYPAEFLFEMTDQTVEPLVIVAK KADTVTTKVKLIKVDQDHNRLEGVGFKLVSVARDGSEKEVPLIGEYRYSSSGQVGRTLYTDKNGEIVVTNLPLGT YRFKEVEPLAGYTVTTMDTDVQLVDHQLVTITVVNQKLPRGNVDFMKVDGRTNTSLQGAMFKVMKEENGHYTPVL QNGKEVVVASGKDGRFRVEGLEYGTYYLWELQAPTGYVQLTSPVSFTIGKDTRKELVTVVKNNKRPRIDVPDTGE ETLYILMLVAILLFGSGYYLTKKTNN

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ORF6_23FTW is a putative sortase. An example of an amino acid sequence of ORF6_23FTW is set forth in SEQ ID NO: 233.

SEQ ID NO: 233

MLIKMVKTKKQKRNNLLLGVVFFIGMAVMAYPLVSRLYYRVESNQQIADFDKEKATLDEADIDERMKLAQAFNDS
LNNVVSGDPWSEEMKKKGRAEYARMLEIHERMGHVEIPVIDVDLPVYAGTAEEVLQQGAGQLEGTSLPIGGNSTH
AVITAHTGLPTÄKMFTDLTKLKVGDKFYVHNIKEVMAYQVDQVKVIEPTNFDDLLIVPGHDYVTLLTCTPYMINT
HRLLVRGHRIPYVAEVEEEFIAANKLSHLYRYLFYVAVGLIVILLWIIRRLRKKKKQPEKALKALKAARKEVKVE
DGQQ

ORF7_23FTW is a putative sortase. An example of an amino acid sequence of ORF7_23FTW is set forth in SEQ ID NO: 234.

SEQ ID NO: 234

MDNSRRSRKKGTKKKKHPLILLLIFLVGFAVAIYPLVSRYYYRIESNEVIKEFDETVSQMDKAELEERWRLAQAF NATLKPSEILDPFTEQEKKKGVSEYANMLKVHERIGYVEIPAIDQEIPMYVGTSEEILQKGAGLLEGASLPVGGE NTHTVVTAHRGLPTAELFSQLDKMKKGDVFYLHVLDQVLAYQVDQILTVEPNDFEPVLIQHGKDYATLLTCTPYM INSHRLLVRGKRIPYTAPIAERNRAVRERGQFWLWLLLAALVMILVLSYGVYRHRRIVKGLEKQLEEHHVKG

ORF8_23FTW is a putative sortase. An example of an amino acid sequence of ORF8_23FTW is set forth in SEQ ID NO: 235.

30 SEQ ID NO: 235

MSKAKLQKLLGYLLMLVALVIPVYCFGQMVLQSLGQVKGHEIFSESVTADSYQEQLQRSLDYNQRLDSQNRIVDP FLAEGYEVNYQVSDDPDAVYGYLSIPSLEIMEPVYLGADYHHLAMGLAHVDGTPLPVEGKGIRSVIAGHRAEPSH VFFRHLDQLKVGDALYYDNGQEIVEYQMMDTEIILPSEWEKLESVSSKNIMTLITCDPIPTFNKRLLVNFERVAV YQKSDPQTAAVARVAFTKEGQSVSRVATSQWLYRGLVVLAFLGILFVLWKLARLLRGK

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As discussed above, a S. pneumoniae AI sequence is present in the 23F Poland 16 S. pneumoniae genome. Examples of S. pneumoniae AI sequences from 23F Poland 16 are set forth below.

ORF2_23FP is a transcriptional regulator. An example of an amino acid sequence of ORF2_23FP is set forth in SEQ ID NO: 236.

SEO ID NO: 236

MLNKYIEKRITDKITILNILLDIRSIELDELSTLTSLQSKSLLSILQELQETFEEELTFNLDTQQVQLIEHHSHQ
TNYYFHQLYNQSTILKILRFFLLQGNQSFNEFTQKEYISIATGYRVRQKCGLLLRSVGLDLVKNQVVGPEYRIRF
LIALLQFHFGIEIYDLNDGSMDWVTHMIVQSNSQLSHELLEITPDEYVHFSILVALTWKRREFPLEFPESKEFEK
LKNLFMYPILMEHCQTYLEPHANMTFTQEELDYIFLVYCSANSSFSKDKWNQEKKTHTIQLILQHTRGKHLLSKF
KNILGNDISNSLSFLTALTFLTRTFLFGLQNLVPYYNYYEHYGIESDKPLYHISKAIVQEWMTEQKIEGVIDQHR
LYLFSLYLTETIFSSLPAIPIFIILNNQADVNLIKSIILRNFTDKVASVTGYNILISPPPSEEHLTEPLIIITTK
EYLPYVKKQYPKGKHHFLTIALDLHVSQQRLIYQTIVDIRKEAFDKRVAMIAKKAHYLL

ORF3_23FP is a cell wall surface protein. An example of an amino acid sequence of ORF3_23FP is set forth in SEQ ID NO: 237.

SEQ ID NO: 237

MKKURK EQKAVACLOUSQUEAFSEL VALAETPETSPAIGKVVIKETGEGGALLGDAVFELKNNTDGTTVSQRT
EAQTGEAIFSNIKPGTYTLTEAQPPVGYKPSTKQWTVEVEKNGRTTVQGEQVENREEALSDQYPQTGTYPDVQTP
YQIIKVDGSEKNGQHKALNPNPYERVIPEGTLSKRIYQVNNLDDNQYGIELTVSGKTTVETKEASTPLDVVILLD
NSNSMSNIRHNHAHRAEKAGEATRALVDKITSNPDNRVALVTYGSTIFDGSEATVEKGVADANGKILNDSALWTF
DRTTFTAKTYNYSFLNLTSDPTDIQTIKDRIPSDAEELNKDKLMYQFGATFTQKALMTADDILTKQARPNSKKVI
FHITDGVPTMSYPINFKYTGTTQSYRTQLNNFKAKTPNSSGILLEDFVTWSADGEHKIVRGDGESYQMFTKKPVT
DQYGVHQILSITSMEQRAKLVSAGYRFYGTDLYLYWRDSILAYPFNSSTDWITNHGDPTTWYYNGNMAQDGYDVF
TVGVGVNGDPGTDEATATRFMQSISSSPDNYTNVADPSQILQELNRYFYTIVNEKKSIENGTITDPMGELIDFQL
GADGRFDPADYTLTANDGSSLVNNVPTGGPQNDGGLLKNAKVFYDTTEKRIRVTGLYLGTGEKVTLTYNVRLNDQ
FVSNKFYDTNGRTTLHPKEVEKNTVRDFPIPKIRDVRKYPEITIPKEKKLGEIEFIKINKNDKKPLRDAVFSLQK
QHPDYPDIYGAIDQNGTYQNVRTGEDGKLTFKNLSDGKYRLFENSEPAGYKPVQNKPIVAFQIVNGEVRDVTSIV
PQDIPAGYEFTNDKHYITNEPIPPKREYPRTGGIGMLPFYLIGCMMMGGVLLYTRKNP

ORF4_23FP is a cell wall surface protein. An example of an amino acid sequence of ORF4_23FP is set forth in SEO ID NO: 238.

15 **SEQ ID NO: 238**

MKSINKFLTMLAALLLTASSLFSAATVFAADNVSTAPDAVTKTLTIHKLLLSEDDLKTWDTNGPKGYDGTQSSLK DLTGVVAEEIPNVYFELQKYNLTDGKEKENLKDDSKWTTVHGGLTTKDGLKIETSTLKGVYRIREDRTKTTYVGP NGQVLTGSKAVPALVTLPLVNNNGTVIDAHVFPKNSYNKPVVDKRIADTLNYNDQNGLSIGTKIPYVVNTTIPSN ATFATSFWSDEMTEGLTYNEDVTITLNNVAMDQADYEVTKGINGFNLKLTEAGLAKINGKDADQKIQITYSATLN SLAVADIPESNDITYHYGNHQDHGNTPKPTKPNNGQITVTKTWDSQPAPEGVKATVQLVNAKTGEKVGAPVELSE NNWTYTWSGLDNSIEYKVEEEYNGYSAEYTVESKGKLGVKNWKDNNPAPINLEEPRVKTYGKKFVKVDQKDTRLE NAQFVVKKADSNKYIAFKSTAQQAADEKAAATAKQKLDAAVAAYTNAADKQAAQALVDQAQQEYNVAYKEAKFGY VEVAGKDEAMVLTSNTDGQFQISGLAAGTYKLEEIKAPEGFAKIDDVEFVVGAGSWNQGEFNYLKDVQKNDATKV VNKKITIPQTGGIGTIIFAVAGAVIMGIAVYAYVKNNKDEDQLA

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ORF5_23FP is a cell wall surface protein. An example of an amino acid sequence of ORF5_23FP is set forth in SEQ ID NO: 239.

SEO ID NO: 239

MTMQKMQKMISRIFFVMALCFSLVWGAHAVQAQEDHTLVLQLENYQEVVSQLPSRDGHRLQVWKLDDSYSYDNRV QIVRDLHSWDENKLSSFKKTSFEMTFLENQIEVSHIPNGLYYVRSIIQTDAVSYPAEFLFEMTDQTVEPLVIVAK KADTVTTKVKLIKVDQDHNRLEGVGFKLVSVARDGSEKEVPLIGEYRYSSSGQVGRTLYTDKNGEIVVTNLPLGT YRFKEVEPLAGYAVTTMDTDVQLVDHQLVTITVVNQKLPRGNVDFMKVDGRTNTSLQGAMFKVMKEENGHYTPVL QNGKEVVVASGKDGRFRVEGLEYGTYYLWELQAPTGYVQLTSPVSFTIGKDTRKELVTVVKNNKRPRIDVPDTGE ETLYILMLVAILLFGSGYYLTKKTNN

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ORF6_23FP is a putative sortase. An example of an amino acid sequence of ORF6_23FP is set forth in SEQ ID NO: 240.

SEQ ID NO: 240

MLIKMAKTKKQKRNNLLLGVVFFIGIAVMAYPLVSRLYYRVESNQQIADFDKEKATLDEADIDERMKLAQAFNDS LNNVVSGDPWSEEMKKKGRAEYARMLEIHERMGHVEIPAIDVDLPVYAGTAEEVLQQGAGHLEGTSLPIGGNSTH AVITAHTGLPTAKMFTDLTKLKVGDKFYVHNIKEVMAYQVDQVKVIEPTNFDDLLIVPGHDYVTLLTCTPYMINT HRLLVRGHRIPYVAEVEEEFIAANKLSHLYRYLFYVAVGLIVILLWIIRRLRKKKRQSERALKALKEATKEVKVE DE

ORF7_23FP is a putative sortase. An example of an amino acid sequence of ORF7_23FP is set forth in SEQ ID NO: 241.

SEO ID NO: 241

MSKSRYSRKKSVKKKKNPFILLLIFLVGLAVAMYPLVSRYYYRIESNEVIKEFDETVSQMDKAELEERWRLAQAF NATLKPSEILDPFTEQEKKKGVSEYANMLKVHERIGYVEIPAIDQEIPMYVGTSEEILQKGAGLLEGASLPVGGE NTHTVVTAHRGLPTAELFSQLDKMKKGDIFYLHVLDQVLAYQVDQIVTVEPNDFEPVLIQHGEDYATLLTCTPYM INSHRLLVRGKRIPYTAPIAERNRAVRERGQFWLWLLLGAMAVILLLLYRVYRNRRIVKGLEKQLEGRHVKD

ORF8_23FP is a putative sortase. An example of an amino acid sequence of ORF8_23FP is set forth in SEQ ID NO: 242.

SEODNO: 2421 C 5 7 E 5 5

MSRTKLRALLGYLLMLVACLIPIYCFGQMVLQSLGQVKGHATFVKSMTTEMYQEQQNHSLAYNQRLASQNRIVDP FLAEGYEVNYQVSDDPDAVYGYLSIPSLEIMEPVYLGADYHHLGMGLAHVDGTPLPLDGTGIRSVIAGHRAEPSH VFFRHLDQLKVGDALYYDNGQEIVEYQMMDTEIILPSEWEKLESVSSKNIMTLITCDPIPTFNKRLLVNFERVAV YQKSDPQTAAVARVAFTKEGQSVSRVATSQWLYRGLVVLAFLGILFVLWKLARLLRGK

Immunogenic compositions of the invention comprising AI antigens may further comprise one or more antigenic agents. Preferred antigens include those listed below. Additionally, the compositions of the present invention may be used to treat or prevent infections caused by any of the below-listed microbes. Antigens for use in the immunogenic compositions include, but are not limited to, one or more of the following set forth below, or antigens derived from one or more of the following set forth below:

Bacterial Antigens

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N. meningitides: a protein antigen from N. meningitides serogroup A, C, W135, Y, and/or B (1-7); an outer-membrane vesicle (OMV) preparation from N. meningitides serogroup B. (8, 9, 10, 11); a saccharide antigen, including LPS, from N. meningitides serogroup A, B, C W135 and/or Y, such as the oligosaccharide from serogroup C (see PCT/US99/09346; PCT IB98/01665; and PCT IB99/00103);

Streptococcus pneumoniae: a saccharide or protein antigen, particularly a saccharide from Streptoccus pneumoniae;

Streptococcus agalactiae: particularly, Group B streptococcus antigens;

Streptococcus pyogenes: particularly, Group A streptococcus antigens;

Enterococcus faecalis or Enterococcus faecium: Particularly a trisaccharide repeat or other Enterococcus derived antigens provided in US Patent No. 6,756,361;

Helicobacter pylori: including: Cag, Vac, Nap, HopX, HopY and/or urease antigen;

Bordetella pertussis: such as petussis holotoxin (PT) and filamentous haemagglutinin (FHA) from B. pertussis, optionally also combination with pertactin and/or agglutinogens 2 and 3 antigen;

Staphylococcus aureus: including S. aureus type 5 and 8 capsular polysaccharides optionally conjugated to nontoxic recombinant *Pseudomonas aeruginosa* exotoxin A, such as StaphVAXTM, or antigens derived from surface proteins, invasins (leukocidin, kinases, hyaluronidase), surface factors that inhibit phagocytic engulfment (capsule, Protein A), carotenoids, catalase production, Protein A, coagulase, clotting factor, and/or membrane-damaging toxins (optionally detoxified) that lyse eukaryotic cell membranes (hemolysins, leukotoxin, leukocidin):

Staphylococcus epidermis: particularly, S. epidermidis slime-associated antigen (SAA);

Staphylococcus saprophyticus: (causing urinary tract infections) particularly the 160 kDa hemagglutinin of S. saprophyticus antigen;

Pseudomonas aeruginosa: particularly, endotoxin A, Wzz protein, P. aeruginosa LPS, more particularly LPS isolated from PAO1 (O5 serotype), and/or Outer Membrane Proteins, including Outer Membrane Proteins F (OprF) (Infect Immun. 2001 May; 69(5): 3510-3515);

Experimental (antifrax): such as B. anthracis antigens (optionally detoxified) from A-components (lethal factor (LF) and edema factor (EF)), both of which can share a common B-component known as protective antigen (PA);

Moraxella catarrhalis: (respiratory) including outer membrane protein antigens (HMW-OMP), C-antigen, and/or LPS;

Yersinia pestis (plague): such as F1 capsular antigen (Infect Immun. 2003 Jan; 71(1)): 374-383, LPS (Infect Immun. 1999 Oct; 67(10): 5395), Yersinia pestis V antigen (Infect Immun. 1997 Nov; 65(11): 4476-4482);

Yersinia enterocolitica (gastrointestinal pathogen): particularly LPS (Infect Immun. 2002 August; 70(8): 4414);

Yersinia pseudotuberculosis: gastrointestinal pathogen antigens;

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Mycobacterium tuberculosis: such as lipoproteins, LPS, BCG antigens, a fusion protein of antigen 85B (Ag85B) and/or ESAT-6 optionally formulated in cationic lipid vesicles (*Infect Immun*. 2004 October; 72(10): 6148), Mycobacterium tuberculosis (Mtb) isocitrate dehydrogenase associated antigens (*Proc Natl Acad Sci U S A.* 2004 Aug 24; 101(34): 12652), and/or MPT51 antigens (*Infect Immun*. 2004 July; 72(7): 3829);

Legionella pneumophila (Legionnairs' Disease): L. pneumophila antigens -- optionally derived from cell lines with disrupted asd genes (Infect Immun. 1998 May; 66(5): 1898);

Rickettsia: including outer membrane proteins, including the outer membrane protein A and/or B (OmpB) (Biochim Biophys Acta. 2004 Nov 1;1702(2):145), LPS, and surface protein antigen (SPA) (J Autoimmun. 1989 Jun;2 Suppl:81);

E. coli: including antigens from enterotoxigenic E. coli (ETEC), enteroaggregative E. coli (EAggEC), diffusely adhering E. coli (DAEC), enteropathogenic E. coli (EPEC), and/or enterohemorrhagic E. coli (EHEC);

Vibrio cholerae: including proteinase antigens, LPS, particularly lipopolysaccharides of Vibrio cholerae II, O1 Inaba O-specific polysaccharides, V. cholera O139, antigens of IEM108 vaccine (*Infect Immun.* 2003 Oct;71(10):5498-504), and/or Zonula occludens toxin (Zot);

Salmonella typhi (typhoid fever): including capsular polysaccharides preferably conjugates (Vi, i.e. vax-TyVi);

Salmonella typhimurium (gastroenteritis): antigens derived therefrom are contemplated for microbial and cancer therapies, including angiogenesis inhibition and modulation of flk;

Listeria monocytogenes (sytemic infections in immunocompromised or elderly people, infections of fetus): antigens derived from L. monocytogenes are preferably used as carriers/vectors for intracytoplasmic delivery of conjugates/associated compositions of the present invention;

Porphyromonas gingivalis: particularly, P. gingivalis outer membrane protein (OMP);

Tetanus: such as tetanus toxoid (TT) antigens, preferably used as a carrier protein in conjunction/conjugated with the compositions of the present invention;

Diphlicial Such as a diphtherial toxoid, preferably CRM₁₉₇, additionally antigens capable of modulating, inhibiting or associated with ADP ribosylation are contemplated for combination/co-administration/conjugation with the compositions of the present invention, the diphtheria toxoids are preferably used as carrier proteins;

Borrelia burgdorferi (Lyme disease): such as antigens associated with P39 and P13 (an integral membrane protein, Infect Immun. 2001 May; 69(5): 3323-3334), VIsE Antigenic Variation Protein (J Clin Microbiol. 1999 Dec; 37(12): 3997);

Haemophilus influenzae B: such as a saccharide antigen therefrom;

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Klebsiella: such as an OMP, including OMP A, or a polysaccharide optionally conjugated to tetanus toxoid;

Neiserria gonorrhoeae: including, a Por (or porin) protein, such as PorB (see Zhu et al., Vaccine (2004) 22:660 – 669), a transferring binding protein, such as TbpA and TbpB (See Price et al., Infection and Immunity (2004) 71(1):277 – 283), a opacity protein (such as Opa), a reduction-modifiable protein (Rmp), and outer membrane vesicle (OMV) preparations (see Plante et al., J Infectious Disease (2000) 182:848 – 855), also see e.g. WO99/24578, WO99/36544, WO99/57280, WO02/079243);

Chlamydia pneumoniae: particularly C. pneumoniae protein antigens;

Chlamydia trachomatis: including antigens derived from serotypes A, B, Ba and C are (agents of trachoma, a cause of blindness), serotypes L_1 , L_2 & L_3 (associated with Lymphogranuloma venereum), and serotypes, D-K;

Treponema pallidum (Syphilis): particularly a TmpA antigen; and

Haemophilus ducreyi (causing chancroid): including outer membrane protein (DsrA).

Where not specifically referenced, further bacterial antigens of the invention may be capsular antigens, polysaccharide antigens or protein antigens of any of the above. Further bacterial antigens may also include an outer membrane vesicle (OMV) preparation. Additionally, antigens include live, attenuated, split, and/or purified versions of any of the aforementioned bacteria. The bacterial or microbial derived antigens of the present invention may be gram-negative or gram-positive and aerobic or anaerobic.

Additionally, any of the above bacterial-derived saccharides (polysaccharides, LPS, LOS or oligosaccharides) can be conjugated to another agent or antigen, such as a carrier protein (for example CRM₁₉₇). Such conjugation may be direct conjugation effected by reductive amination of carbonyl moieties on the saccharide to amino groups on the protein, as provided in US Patent No. 5,360,897 and Can J Biochem Cell Biol. 1984 May;62(5):270-5. Alternatively, the saccharides can be conjugated through a linker, such as, with succinamide or other linkages provided in Bioconjugate Techniques, 1996 and CRC, Chemistry of Protein Conjugation and Cross-Linking, 1993.

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Influenza: including whole viral particles (attenuated), split, or subunit comprising hemagglutinin (HA) and/or neuraminidase (NA) surface proteins, the influenza antigens may be derived from chicken embryos or propogated on cell culture, and/or the influenza antigens are derived from influenza type A, B, and/or C, among others;

Respiratory syncytial virus (RSV): including the F protein of the A2 strain of RSV (J Gen Virol. 2004 Nov; 85(Pt 11):3229) and/or G glycoprotein;

Parainfluenza virus (PIV): including PIV type 1, 2, and 3, preferably containing hemagglutinin, neuraminidase and/or fusion glycoproteins;

Poliovirus: including antigens from a family of picornaviridae, preferably poliovirus antigens such as OPV or, preferably IPV;

Measles: including split measles virus (MV) antigen optionally combined with the Protollin and or antigens present in MMR vaccine;

Mumps: including antigens present in MMR vaccine;

Rubella: including antigens present in MMR vaccine as well as other antigens from Togaviridae, including dengue virus;

Rabies: such as lyophilized inactivated virus (RabAvert™);

Flaviviridae viruses: such as (and antigens derived therefrom) yelow fever virus, Japanese encephalitis virus, dengue virus (types 1, 2, 3, or 4), tick borne encephalitis virus, and West Nile virus;

Caliciviridae; antigens therefrom;

HIV: including HIV-1 or HIV-2 strain antigens, such as gag (p24gag and p55gag), env (gp160 and gp41), pol, tat, nef, rev vpu, miniproteins, (preferably p55 gag and gp140v delete) and antigens from the isolates HIV_{IIIb}, HIV_{SF2}, HIV_{LAV}, HIV_{LAI}, HIV_{MN}, HIV-1_{CM235}, HIV-1_{US4}, HIV-2; simian immunodeficiency virus (SIV) among others;

Rotavirus: including VP4, VP5, VP6, VP7, VP8 proteins (Protein Expr Purif. 2004 Dec;38(2):205) and/or NSP4;

Pestivirus: such as antigens from classical porcine fever virus, bovine viral diarrhoea virus, and/or border disease virus;

Parvovirus: such as parvovirus B19;

Coronavirus: including SARS virus antigens, particularly spike protein or proteases therefrom, as well as antigens included in WO 04/92360;

Hepatitis A virus: such as inactivated virus;

Hepatitis B virus: such as the surface and/or core antigens (sAg), as well as the presurface sequences, pre-S1 and pre-S2 (formerly called pre-S), as well as combinations of the above, such as sAg/pre-S1, sAg/pre-S2, sAg/pre-S1/pre-S2, and pre-S1/pre-S2, (see, e.g., AHBV Vaccines - Human Vaccines and Vaccination, pp. 159-176; and U.S. Patent Nos. 4,722,840, 5,098,704, 5,324,513;

Beathes let al., J. Virol. (1995) 69:6833-6838, Birnbaum et al., J. Virol. (1990) 64:3319-3330; and Zhou et al., J. Virol. (1991) 65:5457-5464);

Hepatitis C virus: such as E1, E2, E1/E2 (see, Houghton et al., Hepatology (1991) 14:381), NS345 polyprotein, NS 345-core polyprotein, core, and/or peptides from the nonstructural regions (International Publication Nos. WO 89/04669; WO 90/11089; and WO 90/14436);

Delta hepatitis virus (HDV): antigens derived therefrom, particularly δ-antigen from HDV (see, e.g., U.S. Patent No. 5,378,814);

Hepatitis E virus (HEV); antigens derived therefrom;

Hepatitis G virus (HGV); antigens derived therefrom;

Varcicella zoster virus: antigens derived from varicella zoster virus (VZV) (J. Gen. Virol. (1986) 67:1759);

Epstein-Barr virus: antigens derived from EBV (Baer et al., Nature (1984) 310:207);

Cytomegalovirus: CMV antigens, including gB and gH (Cytomegaloviruses (J.K. McDougall, ed., Springer-Verlag 1990) pp. 125-169);

Herpes simplex virus: including antigens from HSV-1 or HSV-2 strains and glycoproteins gB, gD and gH (McGeoch et al., J. Gen. Virol. (1988) 69:1531 and U.S. Patent No. 5,171,568);

Human Herpes Virus: antigens derived from other human herpesviruses such as HHV6 and HHV7; and

HPV: including antigens associated with or derived from human papillomavirus (HPV), for example, one or more of E1 – E7, L1, L2, and fusions thereof, particularly the compositions of the invention may include a virus-like particle (VLP) comprising the L1 major capsid protein, more particular still, the HPV antigens are protective against one or more of HPV serotypes 6, 11, 16 and/or 18.

Further provided are antigens, compostions, methods, and microbes included in *Vaccines*, 4th Edition (Plotkin and Orenstein ed. 2004); *Medical Microbiology* 4th Edition (Murray et al. ed. 2002); *Virology*, 3rd Edition (W.K. Joklik ed. 1988); *Fundamental Virology*, 2nd Edition (B.N. Fields and D.M. Knipe, eds. 1991), which are contemplated in conjunction with the compositions of the present invention.

Additionally, antigens include live, attenuated, split, and/or purified versions of any of the aforementioned viruses.

Fungal Antigens

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Fungal antigens for use herein, associated with vaccines include those described in: U.S. Pat. Nos. 4,229,434 and 4,368,191 for prophylaxis and treatment of trichopytosis caused by Trichophyton mentagrophytes; U.S. Pat. Nos. 5,277,904 and 5,284,652 for a broad spectrum dermatophyte vaccine for the prophylaxis of dermatophyte infection in animals, such as guinea pigs, cats, rabbits, horses and lambs, these antigens comprises a suspension of killed *T. equinum*, T. mentagrophytes (var. granulare), *M. canis* and/or *M. gypseum* in an effective amount optionally combined with an adjuvant;

U.S. Patl Nos. 5,458,278 and 6,132,738 for a ringworm vaccine comprising an effective amount of a homogenized, formaldehyde-killed fungi, i.e., *Microsporum canis* culture in a carrier; U.S. Pat. No. 5,948,413 involving extracellular and intracellular proteins for pythiosis. Additional antigens identified within antifungal vaccines include Ringvac bovis LTF-130 and Bioveta.

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Further, fungal antigens for use herein may be derived from Dermatophytres, including: Epidermophyton floccusum, Microsporum audouini, Microsporum canis, Microsporum distortum, Microsporum equinum, Microsporum gypsum, Microsporum nanum, Trichophyton concentricum, Trichophyton equinum, Trichophyton gallinae, Trichophyton gypseum, Trichophyton mentagrophytes, Trichophyton quinckeanum, Trichophyton rubrum, Trichophyton schoenleini, Trichophyton tonsurans, Trichophyton verrucosum, T. verrucosum var. album, var. discoides, var. ochraceum, Trichophyton violaceum, and/or Trichophyton faviforme.

Fungal pathogens for use as antigens or in derivation of antigens in conjunction with the compositions of the present invention comprise Aspergillus fumigatus, Aspergillus flavus, Aspergillus niger, Aspergillus nidulans, Aspergillus terreus, Aspergillus sydowi, Aspergillus flavatus, Aspergillus glaucus, Blastoschizomyces capitatus, Candida albicans, Candida enolase, Candida tropicalis, Candida glabrata, Candida krusei, Candida parapsilosis, Candida stellatoidea, Candida kusei, Candida parakwsei, Candida lusitaniae, Candida pseudotropicalis, Candida guilliermondi, Cladosporium carrionii, Coccidioides immitis, Blastomyces dermatidis, Cryptococcus neoformans, Geotrichum clavatum, Histoplasma capsulatum, Klebsiella pneumoniae, Paracoccidioides brasiliensis, Pneumocystis carinii, Pythiumn insidiosum, Pityrosporum ovale, Sacharomyces cerevisae, Saccharomyces boulardii, Saccharomyces pombe, Scedosporium apiosperum, Sporothrix schenckii, Trichosporon beigelii, Toxoplasma gondii, Penicillium marneffei, Malassezia spp., Fonsecaea spp., Wangiella spp., Sporothrix spp., Basidiobolus spp., Conidiobolus spp., Rhizopus spp, Mucor spp, Absidia spp, Mortierella spp, Cunninghamella spp, and Saksenaea spp.

Other fungi from which antigens are derived include Alternaria spp, Curvularia spp, Helminthosporium spp, Fusarium spp, Aspergillus spp, Penicillium spp, Monolinia spp, Rhizoctonia spp, Paecilomyces spp, Pithomyces spp, and Cladosporium spp.

Processes for producing a fungal antigens are well known in the art (see US Patent No. 6,333,164). In a preferred method a solubilized fraction extracted and separated from an insoluble fraction obtainable from fungal cells of which cell wall has been substantially removed or at least partially removed, characterized in that the process comprises the steps of: obtaining living fungal cells; obtaining fungal cells of which cell wall has been substantially removed or at least partially removed; bursting the fungal cells of which cell wall has been substantially removed or at least partially removed; obtaining an insoluble fraction; and extracting and separating a solubilized fraction from the insoluble fraction.

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In particular embodiments, microbes (bacteria, viruses and/or fungi) against which the present compositions and methods can be implement include those that cause sexually transmitted diseases (STDs) and/or those that display on their surface an antigen that can be the target or antigen composition of the invention. In a preferred embodiment of the invention, compositions are combined with antigens derived from a viral or bacterial STD. Antigens derived from bacteria or viruses can be administered in conjunction with the compositions of the present invention to provide protection against at least one of the following STDs, among others: chlamydia, genital herpes, hepatitis (particularly HCV), genital warts, gonorrhoea, syphilis and/or chancroid (See, WO00/15255).

In another embodiment the compositions of the present invention are co-administered with an antigen for the prevention or treatment of an STD.

Antigens derived from the following viruses associated with STDs, which are described in greater detail above, are preferred for co-administration with the compositions of the present invention: hepatitis (particularly HCV), HPV, HIV, or HSV.

Additionally, antigens derived from the following bacteria associated with STDs, which are described in greater detail above, are preferred for co-administration with the compositions of the present invention: Neiserria gonorrhoeae, Chlamydia pneumoniae, Chlamydia trachomatis, Treponema pallidum, or Haemophilus ducreyi.

Respiratory Antigens

The antigen may be a respiratory antigen and could further be used in an immunogenic composition for methods of preventing and/or treating infection by a respiratory pathogen, including a virus, bacteria, or fungi such as respiratory syncytial virus (RSV), PIV, SARS virus, influenza, *Bacillus anthracis*, particularly by reducing or preventing infection and/or one or more symptoms of respiratory virus infection. A composition comprising an antigen described herein, such as one derived from a respiratory virus, bacteria or fungus is administered in conjunction with the compositions of the present invention to an individual which is at risk of being exposed to that particular respiratory microbe, has been exposed to a respiratory microbe or is infected with a respiratory virus, bacteria or fungus. The composition(s) of the present invention is/are preferably coadministered at the same time or in the same formulation with an antigen of the respiratory pathogen. Administration of the composition results in reduced incidence and/or severity of one or more symptoms of respiratory infection.

Pediatric/Geriatric Antigens

In one embodiment the compositions of the present invention are used in conjunction with an antigen for treatment of a pediatric population, as in a pediatric antigen. In a more particular embodiment the pediatric population is less than about 3 years old, or less than about 2 years, or less than about 1 years old. In another embodiment the pediatric antigen (in conjunction with the composition of the present invention) is administered multiple times over at least 1, 2, or 3 years.

In another embodiment the compositions of the present invention are used in conjunction with an antigen for treatment of a geriatric population, as in a geriatric antigen.

Other Antigens

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Other antigens for use in conjunction with the compositions of the present include hospital acquired (nosocomial) associated antigens.

In another embodiment, parasitic antigens are contemplated in conjunction with the compositions of the present invention. Examples of parasitic antigens include those derived from organisms causing malaria and/or Lyme disease.

In another embodiment, the antigens in conjunction with the compositions of the present invention are associated with or effective against a mosquito born illness. In another embodiment, the antigens in conjunction with the compositions of the present invention are associated with or effective against encephalitis. In another embodiment the antigens in conjunction with the compositions of the present invention are associated with or effective against an infection of the nervous system.

In another embodiment, the antigens in conjunction with the compositions of the present invention are antigens transmissible through blood or body fluids.

Antigen Formulations

In other aspects of the invention, methods of producing microparticles having adsorbed antigens are provided. The methods comprise: (a) providing an emulsion by dispersing a mixture comprising (i) water, (ii) a detergent, (iii) an organic solvent, and (iv) a biodegradable polymer selected from the group consisting of a poly(α-hydroxy acid), a polyhydroxy butyric acid, a polycaprolactone, a polyorthoester, a polyanhydride, and a polycyanoacrylate. The polymer is typically present in the mixture at a concentration of about 1% to about 30% relative to the organic solvent, while the detergent is typically present in the mixture at a weight-to-weight detergent-to-polymer ratio of from about 0.00001:1 to about 0.1:1 (more typically about 0.0001:1 to about 0.1:1, about 0.001:1 to about 0.1:1); (b) removing the organic solvent from the emulsion; and (c) adsorbing an antigen on the surface of the microparticles. In certain embodiments, the biodegradable polymer is present at a concentration of about 3% to about 10% relative to the organic solvent.

Microparticles for use herein will be formed from materials that are sterilizable, non-toxic and biodegradable. Such materials include, without limitation, $poly(\alpha-hydroxy acid)$, polyhydroxybutyric acid, polycaprolactone, polyorthoester, polyanhydride, PACA, and polycyanoacrylate. Preferably, microparticles for use with the present invention are derived from a poly(α -hydroxy acid), in particular, from a poly(lactide) ("PLA") or a copolymer of D,L-lactide and glycolide or glycolic acid, such as a poly(D,L-lactide-co-glycolide) ("PLG" or "PLGA"), or a copolymer of D,L-lactide and caprolactone. The microparticles may be derived from any of various polymeric starting materials which have a variety of molecular weights and, in the case of the copolymers such as PLG, a variety of lactide:glycolide ratios, the selection of which will be largely a

matter of chaice depending in part on the coadministered macromolecule. These parameters are discussed more fully below.

Further antigens may also include an outer membrane vesicle (OMV) preparation.

Additional formulation methods and antigens (especially tumor antigens) are provided in U.S.

5 Patent Serial No. 09/581,772.

Antigen References

The following references include antigens useful in conjunction with the compositions of the present invention:

- 10 1 International patent application WO99/24578
 - 2 International patent application WO99/36544.
 - 3 International patent application WO99/57280.
 - 4 International patent application WO00/22430.
 - 5 Tettelin et al. (2000) Science 287:1809-1815.
- 15 6 International patent application WO96/29412.
 - 7 Pizza et al. (2000) Science 287:1816-1820.
 - 8 PCT WO 01/52885.
 - 9 Bjune et al. (1991) Lancet 338(8775).
 - 10 Fuskasawa et al. (1999) Vaccine 17:2951-2958.
- 20 11 Rosenqist et al. (1998) Dev. Biol. Strand 92:323-333.
 - 12 Constantino et al. (1992) Vaccine 10:691-698.
 - 13 Constantino et al. (1999) Vaccine 17:1251-1263.
 - 14 Watson (2000) Pediatr Infect Dis J 19:331-332.
 - 15 Rubin (20000) Pediatr Clin North Am 47:269-285, v.
- 25 16 Jedrzejas (2001) Microbiol Mol Biol Rev 65:187-207.
 - 17 International patent application filed on 3rd July 2001 claiming priority from GB-0016363.4;WO 02/02606; PCT IB/01/00166.
 - 18 Kalman et al. (1999) Nature Genetics 21:385-389.
 - 19 Read et al. (2000) Nucleic Acids Res 28:1397-406.
- 30 20 Shirai et al. (2000) J. Infect. Dis 181(Suppl 3):S524-S527.
 - 21 International patent application WO99/27105.
 - 22 International patent application WO00/27994.
 - 23 International patent application WO00/37494.
 - 24 International patent application WO99/28475.
- 35 25 Bell (2000) Pediatr Infect Dis J 19:1187-1188.
 - 26 Iwarson (1995) APMIS 103:321-326.
 - 27 Gerlich et al. (1990) Vaccine 8 Suppl:S63-68 & 79-80.
 - 28 Hsu et al. (1999) Clin Liver Dis 3:901-915.
 - 29 Gastofsson et al. (1996) N. Engl. J. Med. 334-:349-355.
- 40 30 Rappuoli et al. (1991) TIBTECH 9:232-238.
 - 31 Vaccines (1988) eds. Plotkin & Mortimer. ISBN 0-7216-1946-0.
 - 32 Del Guidice et al. (1998) Molecular Aspects of Medicine 19:1-70.
 - 33 International patent application WO93/018150.
 - 34 International patent application WO99/53310.
- 45 35 International patent application WO98/04702.
 - 36 Ross et al. (2001) Vaccine 19:135-142.
 - 37 Sutter et al. (2000) Pediatr Clin North Am 47:287-308.
 - 38 Zimmerman & Spann (1999) Am Fan Physician 59:113-118, 125-126.
 - 39 Dreensen (1997) Vaccine 15 Suppl"S2-6.
- 50 40 MMWR Morb Mortal Wkly rep 1998 Jan 16:47(1):12, 9.
 - 41 McMichael (2000) Vaccine19 Suppl 1:S101-107.

- 42 Schuchat (1999) Lancer 353(9146):51-6.
 43 GB patent applications 0026333.5, 0028727.6 & 0105640.7.
 - 44 Dale (1999) Infect Disclin North Am 13:227-43, viii.
 - 45 Ferretti et al. (2001) PNAS USA 98: 4658-4663.
- 5 46 Kuroda et al. (2001) Lancet 357(9264):1225-1240; see also pages 1218-1219.
 - 47 Ramsay et al. (2001) Lancet 357(9251):195-196.
 - 48 Lindberg (1999) Vaccine 17 Suppl 2: S28-36.
 - 49 Buttery & Moxon (2000) JR Coil Physicians Long 34:163-168.
 - 50 Ahmad & Chapnick (1999) Infect Dis Clin North Am 13:113-133, vii.
- 10 51 Goldblatt (1998) J. Med. Microbiol. 47:663-567.
 - 52 European patent 0 477 508.
 - 53 U.S. Patent No. 5,306,492.
 - 54 International patent application WO98/42721.
 - 55 Conjugate Vaccines (eds. Cruse et al.) ISBN 3805549326, particularly vol. 10:48-114.
- 15 56 Hermanson (1996) Bioconjugate Techniques ISBN: 012323368 & 012342335X.
 - 57 European patent application 0372501.
 - 58 European patent application 0378881.
 - 59 European patent application 0427347.
 - 60 International patent application WO93/17712.
- 20 61 International patent application WO98/58668.
 - 62 European patent application 0471177.
 - 63 International patent application WO00/56360.
 - 64 International patent application WO00/67161.
- 25 The contents of all of the above cited patents, patent applications and journal articles are incorporated by reference as if set forth fully herein.

There may be an upper limit to the number of Gram positive bacterial proteins which will be in the compositions of the invention. Preferably, the number of Gram positive bacterial proteins in a composition of the invention is less than 20, less than 19, less than 18, less than 17, less than 16, less than 15, less than 14, less than 13, less than 12, less than 11, less than 10, less than 9, less than 8, less than 7, less than 6, less than 5, less than 4, or less than 3. Still more preferably, the number of Gram positive bacterial proteins in a composition of the invention is less than 6, less than 5, or less than 4. Still more preferably, the number of Gram positive bacterial proteins in a composition of the invention is 3.

The Gram positive bacterial proteins and polynucleotides used in the invention are preferably isolated, i.e., separate and discrete, from the whole organism with which the molecule is found in nature or, when the polynucleotide or polypeptide is not found in nature, is sufficiently free of other biological macromolecules so that the polynucleotide or polypeptide can be used for its intended purpose.

40 Fusion Proteins: GBS AI sequences

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The GBS AI proteins used in the invention may be present in the composition as individual separate polypeptides, but it is preferred that at least two (i.e. 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18) of the antigens are expressed as a single polypeptide chain (a "hybrid" or "fusion" polypeptide). Such fusion polypeptides offer two principal advantages: first, a polypeptide that may be unstable or poorly expressed on its own can be assisted by adding a suitable fusion partner that

overcomes the problem; second, commercial manufacture is simplified as only one expression and purification need be employed in order to produce two polypeptides which are both antigenically useful.

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The fusion polypeptide may comprise one or more AI polypeptide sequences. Preferably, the fusion comprises an AI surface protein sequence. Preferably, the fusion polypeptide includes one or more of GBS 80, GBS 104, and GBS 67. Most preferably, the fusion peptide includes a polypeptide sequence from GBS 80. Accordingly, the invention includes a fusion peptide comprising a first amino acid sequence and a second amino acid sequence, wherein said first and second amino acid sequences are selected from a GBS AI surface protein or a fragment thereof. Preferably, the first and second amino acid sequences in the fusion polypeptide comprise different epitopes.

Hybrids (or fusions) consisting of amino acid sequences from two, three, four, five, six, seven, eight, nine, or ten GBS antigens are preferred. In particular, hybrids consisting of amino acid sequences from two, three, four, or five GBS antigens are preferred.

Different hybrid polypeptides may be mixed together in a single formulation. Within such combinations, a GBS antigen may be present in more than one hybrid polypeptide and/or as a non-hybrid polypeptide. It is preferred, however, that an antigen is present either as a hybrid or as a non-hybrid, but not as both.

Hybrid polypeptides can be represented by the formula NH_2 -A- $\{-X-L-\}_n$ -B-COOH, wherein: X is an amino acid sequence of a GBS AI protein or a fragment thereof; L is an optional linker amino acid sequence; A is an optional N-terminal amino acid sequence; B is an optional C-terminal amino acid sequence; and n is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15.

If a -X- moiety has a leader peptide sequence in its wild-type form, this may be included or omitted in the hybrid protein. In some embodiments, the leader peptides will be deleted except for that of the -X- moiety located at the N-terminus of the hybrid protein *i.e.* the leader peptide of X_1 will be retained, but the leader peptides of $X_2 \dots X_n$ will be omitted. This is equivalent to deleting all leader peptides and using the leader peptide of X_1 as moiety -A-.

For each n instances of $\{-X-L-\}$, linker amino acid sequence -L- may be present or absent. For instance, when n=2 the hybrid may be NH₂-X₁-L₁-X₂-L₂-COOH, NH₂-X₁-X₂-COOH, NH₂-X₁-X₂-COOH, NH₂-X₁-X₂-L₂-COOH, etc. Linker amino acid sequence(s) -L- will typically be short (e.g. 20 or fewer amino acids i.e. 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples comprise short peptide sequences which facilitate cloning, poly-glycine linkers (i.e. comprising Gly_n where n=2, 3, 4, 5, 6, 7, 8, 9, 10 or more), and histidine tags (i.e. His_n where n=3, 4, 5, 6, 7, 8, 9, 10 or more). Other suitable linker amino acid sequences will be apparent to those skilled in the art. A useful linker is GSGGGG, with the Gly-Ser dipeptide being formed from a BamHI restriction site, thus aiding cloning and manipulation, and the (Gly)₄ tetrapeptide being a typical poly-glycine linker.

-A- is an optional N-terminal amino acid sequence. This will typically be short (e.g. 40 or fewer amino acids i.e. 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19,

18, 17, 16, 15, 14, 12, 12, 14, 19, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples include leader sequences to direct protein trafficking, or short peptide sequences which facilitate cloning or purification (e.g. histidine tags i.e. His, where n = 3, 4, 5, 6, 7, 8, 9, 10 or more). Other suitable N-terminal amino acid sequences will be apparent to those skilled in the art. If X_1 lacks its own N-terminus methionine, -A-is preferably an oligopeptide (e.g. with 1, 2, 3, 4, 5, 6, 7 or 8 amino acids) which provides a N-terminus methionine.

-B- is an optional C-terminal amino acid sequence. This will typically be short (e.g. 40 or fewer amino acids i.e. 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples include sequences to direct protein trafficking, short peptide sequences which facilitate cloning or purification (e.g. comprising histidine tags i.e. His, where n = 3, 4, 5, 6, 7, 8, 9, 10 or more), or sequences which enhance protein stability. Other suitable C-terminal amino acid sequences will be apparent to those skilled in the art.

Most preferably, n is 2 or 3.

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Fusion Proteins: Gram positive bacteria AI sequences

The Gram positive bacteria AI proteins used in the invention may be present in the composition as individual separate polypeptides, but it is preferred that at least two (i.e. 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18) of the antigens are expressed as a single polypeptide chain (a "hybrid" or "fusion" polypeptide). Such fusion polypeptides offer two principal advantages: first, a polypeptide that may be unstable or poorly expressed on its own can be assisted by adding a suitable fusion partner that overcomes the problem; second, commercial manufacture is simplified as only one expression and purification need be employed in order to produce two polypeptides which are both antigenically useful.

The fusion polypeptide may comprise one or more AI polypeptide sequences. Preferably, the fusion comprises an AI surface protein sequence. Accordingly, the invention includes a fusion peptide comprising a first amino acid sequence and a second amino acid sequence, wherein said first and second amino acid sequences are selected from a Gram positive bacteria AI protein or a fragment thereof. Preferably, the first and second amino acid sequences in the fusion polypeptide comprise different epitopes.

Hybrids (or fusions) consisting of amino acid sequences from two, three, four, five, six, seven, eight, nine, or ten Gram positive bacteria antigens are preferred. In particular, hybrids consisting of amino acid sequences from two, three, four, or five Gram positive bacteria antigens are preferred.

Different hybrid polypeptides may be mixed together in a single formulation. Within such combinations, a Gram positive bacteria AI sequence may be present in more than one hybrid polypeptide and/or as a non-hybrid polypeptide. It is preferred, however, that an antigen is present either as a hybrid or as a non-hybrid, but not as both.

Hybrid polypeptides can be represented by the formula NH_2 -A- $\{-X-L-\}_n$ -B-COOH, wherein: X is an amino acid sequence of a Gram positive bacteria AI sequence or a fragment thereof; L is an -226-

optional linker amino acid sequence; A is an optional N-terminal amino acid sequence; B is an optional C-terminal amino acid sequence; and n is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15.

If a -X- moiety has a leader peptide sequence in its wild-type form, this may be included or omitted in the hybrid protein. In some embodiments, the leader peptides will be deleted except for that of the -X- moiety located at the N-terminus of the hybrid protein *i.e.* the leader peptide of X_1 will be retained, but the leader peptides of $X_2 \dots X_n$ will be omitted. This is equivalent to deleting all leader peptides and using the leader peptide of X_1 as moiety -A-.

-A- is an optional N-terminal amino acid sequence. This will typically be short (e.g. 40 or fewer amino acids i.e. 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples include leader sequences to direct protein trafficking, or short peptide sequences which facilitate cloning or purification (e.g. histidine tags i.e. His_n where n = 3, 4, 5, 6, 7, 8, 9, 10 or more). Other suitable N-terminal amino acid sequences will be apparent to those skilled in the art. If X_1 lacks its own N-terminus methionine, -A-is preferably an oligopeptide (e.g. with 1, 2, 3, 4, 5, 6, 7 or 8 amino acids) which provides a N-terminus methionine.

-B- is an optional C-terminal amino acid sequence. This will typically be short (e.g. 40 or fewer amino acids i.e. 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples include sequences to direct protein trafficking, short peptide sequences which facilitate cloning or purification (e.g. comprising histidine tags i.e. His, where n = 3, 4, 5, 6, 7, 8, 9, 10 or more), or sequences which enhance protein stability. Other suitable C-terminal amino acid sequences will be apparent to those skilled in the art.

Most preferably, n is 2 or 3.

Antibodies: GBS AI sequences

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The GBS AI proteins of the invention may also be used to prepare antibodies specific to the GBS AI proteins. The antibodies are preferably specific to the an oligomeric or hyper-oligomeric form of an AI protein. The invention also includes combinations of antibodies specific to GBS AI proteins selected to provide protection against an increased range of GBS serotypes and strain isolates. For example, a combination may comprise a first and second antibody, wherein said first -227-

antibody is specific to a first GBS AI protein and said second antibody is specific to a second GBS AI protein. Preferably, the nucleic acid sequence encoding said first GBS AI protein is not present in a GBS genome comprising a polynucleotide sequence encoding for said second GBS AI protein. Preferably, the nucleic acid sequence encoding said first and second GBS AI proteins are present in the genomes of multiple GBS serotypes and strain isolates.

The GBS specific antibodies of the invention include one or more biological moieties that, through chemical or physical means, can bind to or associate with an epitope of a GBS polypeptide. The antibodies of the invention include antibodies which specifically bind to a GBS AI protein. The invention includes antibodies obtained from both polyclonal and monoclonal preparations, as well as the following: hybrid (chimeric) antibody molecules (see, for example, Winter et al. (1991) Nature 349; 293-299; and US Patent No. 4,816,567; F(ab'), and F(ab) fragments; F, molecules (non-covalent heterodimers, see, for example, Inbar et al. (1972) Proc Natl Acad Sci USA 69:2659-2662; and Ehrlich et al. (1980) Biochem 19:4091-4096); single-chain Fv molecules (sFv) (see, for example, Huston et al. (1988) Proc Natl Acad Sci USA 85:5897-5883); dimeric and trimeric antibody fragment constructs; minibodies (see, e.g., Pack et al. (1992) Biochem 31:1579-1584; Cumber et al. (1992) J Immunology 149B: 120-126); humanized antibody molecules (see, for example, Riechmann et al. (1988) Nature 332:323-327; Verhoeyan et al. (1988) Science 239:1534-1536; and U.K. Patent Publication No. GB 2,276,169, published 21 September 1994); and, any functional fragments obtained from such molecules, wherein such fragments retain immunological binding properties of the parent antibody molecule. The invention further includes antibodies obtained through nonconventional processes, such as phage display.

Preferably, the GBS specific antibodies of the invention are monoclonal antibodies. Monoclonal antibodies of the invention include an antibody composition having a homogeneous antibody population. Monoclonal antibodies of the invention may be obtained from murine hybridomas, as well as human monoclonal antibodies obtained using human rather than murine hybridomas. See, e.g., Cote, et al. Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, 1985, p 77.

The antibodies of the invention may be used in diagnostic applications, for example, to detect the presence or absence of GBS in a biological sample. The antibodies of the invention may also be used in the prophylactic or therapeutic treatment of GBS infection.

Antibodies: Gram positive bacteria AI sequences

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The Gram positive bacteria AI proteins of the invention may also be used to prepare antibodies specific to the Gram positive bacteria AI proteins. The antibodies are preferably specific to the an oligomeric or hyper-oligomeric form of an AI protein. The invention also includes combinations of antibodies specific to Gram positive bacteria AI proteins selected to provide protection against an increased range of Gram positive bacteria genus, species, serotypes and strain isolates.

For example, a combination may comprise a first and second antibody, wherein said first antibody is specific to a first Gram positive bacteria AI protein and said second antibody is specific to a second Gram positive bacteria AI protein. Preferably, the nucleic acid sequence encoding said first Gram positive bacteria AI protein is not present in a Gram positive bacterial genome comprising a polynucleotide sequence encoding for said second Gram positive bacteria AI protein. Preferably, the nucleic acid sequence encoding said first and second Gram positive bacteria AI proteins are present in the genomes of multiple Gram positive bacteria genus, species, serotypes or strain isolates.

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As an example of an instance where the combination of antibodies provides protection against an increased range of bacteria serotypes, the first antibody may be specific to a first GAS AI protein and the second antibody may be specific to a second GAS AI protein. The first GAS AI protein may comprise a GAS AI-1 surface protein, while the second GAS AI protein may comprise a GAS AI-2 or AI-3 surface protein.

As an example of an instance where the combination of antibodies provides protection against an increased range of bacterial species, the first antibody may be specific to a GBS AI protein and the second antibody may be specific to a GAS AI protein. Alternatively, the first antibody may be specific to a GAS AI protein and the second antibody may be specific to a S. pneumoniae AI protein.

The Gram positive specific antibodies of the invention include one or more biological moieties that, through chemical or physical means, can bind to or associate with an epitope of a Gram positive bacteria AI polypeptide. The antibodies of the invention include antibodies which specifically bind to a Gram positive bacteria AI protein. The invention includes antibodies obtained from both polyclonal and monoclonal preparations, as well as the following: hybrid (chimeric) antibody molecules (see, for example, Winter et al. (1991) Nature 349: 293-299; and US Patent No. 4,816,567; F(ab')₂ and F(ab) fragments; F_v molecules (non-covalent heterodimers, see, for example, Inbar et al. (1972) Proc Natl Acad Sci USA 69:2659-2662; and Ehrlich et al. (1980) Biochem 19:4091-4096); single-chain Fv molecules (sFv) (see, for example, Huston et al. (1988) Proc Natl Acad Sci USA 85:5897-5883); dimeric and trimeric antibody fragment constructs; minibodies (see, e.g., Pack et al. (1992) Biochem 31:1579-1584; Cumber et al. (1992) J Immunology 149B: 120-126); humanized antibody molecules (see, for example, Riechmann et al. (1988) Nature 332:323-327; Verhoeyan et al. (1988) Science 239:1534-1536; and U.K. Patent Publication No. GB 2,276,169, published 21 September 1994); and, any functional fragments obtained from such molecules, wherein such fragments retain immunological binding properties of the parent antibody molecule. The invention further includes antibodies obtained through non-conventional processes, such as phage display.

Preferably, the Gram positive specific antibodies of the invention are monoclonal antibodies. Monoclonal antibodies of the invention include an antibody composition having a homogeneous antibody population. Monoclonal antibodies of the invention may be obtained from murine hybridomas, as well as human monoclonal antibodies obtained using human rather than murine

hybridomas. See e.g. Cote, et al. Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, 1985, p

The antibodies of the invention may be used in diagnostic applications, for example, to detect the presence or absence of Gram positive bacteria in a biological sample. The antibodies of the invention may also be used in the prophylactic or therapeutic treatment of Gram positive bacteria infection.

Nucleic Acids

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The invention provides nucleic acids encoding the Gram positive bacteria sequences and/or the hybrid fusion polypeptides of the invention. The invention also provides nucleic acid encoding the GBS antigens and/or the hybrid fusion polypeptides of the invention. Furthermore, the invention provides nucleic acid which can hybridise to these nucleic acids, preferably under "high stringency" conditions (e.g. 65°C in a 0.1xSSC, 0.5% SDS solution).

Polypeptides of the invention can be prepared by various means (e.g. recombinant expression, purification from cell culture, chemical synthesis, etc.) and in various forms (e.g. native, fusions, non-glycosylated, lipidated, etc.). They are preferably prepared in substantially pure form (i.e. substantially free from other GAS or host cell proteins).

Nucleic acid according to the invention can be prepared in many ways (e.g. by chemical synthesis, from genomic or cDNA libraries, from the organism itself, etc.) and can take various forms (e.g. single stranded, double stranded, vectors, probes, etc.). They are preferably prepared in substantially pure form (i.e. substantially free from other GBS or host cell nucleic acids).

The term "nucleic acid" includes DNA and RNA, and also their analogues, such as those containing modified backbones (e.g. phosphorothioates, etc.), and also peptide nucleic acids (PNA), etc. The invention includes nucleic acid comprising sequences complementary to those described above (e.g. for antisense or probing purposes).

The invention also provides a process for producing a polypeptide of the invention, comprising the step of culturing a host cell transformed with nucleic acid of the invention under conditions which induce polypeptide expression.

The invention provides a process for producing a polypeptide of the invention, comprising the step of synthesising at least part of the polypeptide by chemical means.

The invention provides a process for producing nucleic acid of the invention, comprising the step of amplifying nucleic acid using a primer-based amplification method (e.g. PCR).

The invention provides a process for producing nucleic acid of the invention, comprising the step of synthesising at least part of the nucleic acid by chemical means.

Purification and Recombinant Expression

The Gram positive bacteria AI proteins of the invention may be isolated from the native Gram positive bacteria, or they may be recombinantly produced, for instance in a heterologous host. For example, the GAS, GBS, and S. pneumoniae antigens of the invention may be isolated from

Streptococcus agalactiae, S. progenes, S. preumoniae, or they may be recombinantly produced, for instance, in a heterologous host. Preferably, the GBS antigens are prepared using a heterologous host.

The heterologous host may be prokaryotic (e.g. a bacterium) or eukaryotic. It is preferably *E.coli*, but other suitable hosts include *Bacillus subtilis*, *Vibrio cholerae*, *Salmonella typhi*, *Salmonella typhimurium*, *Neisseria lactamica*, *Neisseria cinerea*, *Mycobacteria* (e.g. *M.tuberculosis*), *S. gordonii*, *L. lactis*, yeasts, *etc*.

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Recombinant production of polypeptides is facilitated by adding a tag protein to the Gram positive bacteria AI sequence to be expressed as a fusion protein comprising the tag protein and the Gram positive bacteria antigen. For example, recombinant production of polypeptides is facilitated by adding a tag protein to the GBS antigen to be expressed as a fusion protein comprising the tag protein and the GBS antigen. Such tag proteins can facilitate purification, detection and stability of the expressed protein. Tag proteins suitable for use in the invention include a polyarginine tag (Arg-tag), polyhistidine tag (His-tag), FLAG-tag, Strep-tag, c-myc-tag, S-tag, calmodulin-binding peptide, cellulose-binding domain, SBP-tag,, chitin-binding domain, glutathione S-transferase-tag (GST), maltose-binding protein, transcription termination anti-terminiantion factor (NusA), *E. coli* thioredoxin (TrxA) and protein disulfide isomerase I (DsbA). Preferred tag proteins include His-tag and GST. A full discussion on the use of tag proteins can be found at Terpe et al., "Overview of tag protein fusions: from molecular and biochemical fundamentals to commercial systems", Appl Microbiol Biotechnol (2003) 60:523 – 533.

After purification, the tag proteins may optionally be removed from the expressed fusion protein, *i.e.*, by specifically tailored enzymatic treatments known in the art. Commonly used proteases include enterokinase, tobacco etch virus (TEV), thrombin, and factor X_a .

GBS polysaccharides

The compositions of the invention may be further improved by including GBS polysaccharides. Preferably, the GBS antigen and the saccharide each contribute to the immunological response in a recipient. The combination is particularly advantageous where the saccharide and polypeptide provide protection from different GBS serotypes.

The combined antigens may be present as a simple combination where separate saccharide and polypeptide antigens are administered together, or they may be present as a conjugated combination, where the saccharide and polypeptide antigens are covalently linked to each other.

Thus the invention provides an immunogenic composition comprising (i) one or more GBS AI proteins and (ii) one or more GBS saccharide antigens. The polypeptide and the polysaccharide may advantageously be covalently linked to each other to form a conjugate.

Between them, the combined polypeptide and saccharide antigens preferably cover (or provide protection from) two or more GBS serotypes (e.g. 2, 3, 4, 5, 6, 7, 8 or more serotypes). The serotypes of the polypeptide and saccharide antigens may or may not overlap. For example, the polypeptide might protect against serogroup II or V, while the saccharide protects against either serogroups Ia, Ib, or III. Preferred combinations protect against the following groups of serotypes:

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(1) serotypes Ia and Ib. (2) serotypes Ia and II, (3) serotypes Ia and III, (4) serotypes Ia and IV, (5) serotypes Ia and V, (6) serotypes Ia and VI, (7) serotypes Ia and VII, (8) serotypes Ia and VIII, (9) serotypes Ib and II, (10) serotypes Ib and III, (11) serotypes Ib and IV, (12) serotypes Ib and V, (13) serotypes Ib and VI, (14) serotypes Ib and VII, (15) serotypes Ib and VIII, (16) serotypes II and III, (17) serotypes II and IV, (18) serotypes II and V, (19) serotypes II and VI, (20) serotypes II and VII, (21) serotypes II and VII, (22) serotypes III and IV, (23) serotypes III and V, (24) serotypes III and VI, (25) serotypes III and VIII, (26) serotypes III and VIII, (27) serotypes IV and V, (28) serotypes IV and VI, (29) serotypes IV and VII, (30) serotypes IV and VIII, (31) serotypes V and VII, (32) serotypes V and VIII, (33) serotypes VI and VIII, (34) serotypes VI and VIII, (35) serotypes VI and VIII, and (36) serotypes VII and VIII.

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Still more preferably, the combinations protect against the following groups of serotypes: (1) serotypes Ia and II, (2) serotypes Ia and V, (3) serotypes Ib and II, (4) serotypes Ib and V, (5) serotypes III and II, and (6) serotypes III and V. Most preferably, the combinations protect against serotypes III and V.

Protection against serotypes II and V is preferably provided by polypeptide antigens. Protection against serotypes Ia, Ib and/or III may be polypeptide or saccharide antigens. Immunogenic compositions and medicaments

Compositions of the invention are preferably immunogenic compositions, and are more preferably vaccine compositions. The pH of the composition is preferably between 6 and 8, preferably about 7. The pH may be maintained by the use of a buffer. The composition may be sterile and/or pyrogen-free. The composition may be isotonic with respect to humans.

Vaccines according to the invention may either be prophylactic (i.e. to prevent infection) or therapeutic (i.e. to treat infection), but will typically be prophylactic. Accordingly, the invention includes a method for the therapeutic or prophylactic treatment of a Gram positive bacteria infection in an animal susceptible to such gram positive bacterial infection comprising administering to said animal a therapeutic or prophylactic amount of the immunogenic composition of the invention. For example, the invention includes a method for the therapeutic or prophylactic treatment of a Streptococcus agalactiae, S. pyogenes, or S. pneumoniae infection in an animal susceptible to streptococcal infection comprising administering to said animal a therapeutic or prophylactic amount of the immunogenic compositions of the invention.

The invention also provides a composition of the invention for use of the compositions described herein as a medicament. The medicament is preferably able to raise an immune response in a mammal (i.e. it is an immunogenic composition) and is more preferably a vaccine.

The invention also provides the use of the compositions of the invention in the manufacture of a medicament for raising an immune response in a mammal. The medicament is preferably a vaccine.

The invention also provides kits comprising one or more containers of compositions of the invention. Compositions can be in liquid form or can be lyophilized, as can individual antigens. Suitable containers for the compositions include, for example, bottles, vials, syringes, and test tubes.

Containers can be formed from a variety of materials, including glass or plastic. A container may have a sterile access port (for example, the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The composition may comprise a first component comprising one or more Gram positive bacteria AI proteins. Preferably, the AI proteins are surface AI proteins. Preferably, the AI surface proteins are in an oligomeric or hyperoligomeric form. For example, the first component comprises a combination of GBS antigens or GAS antigens, or S. pneumoniae antigens. Preferably said combination includes GBS 80. Preferably GBS 80 is present in an oligomeric or hyperoligomeric form.

The kit can further comprise a second container comprising a pharmaceutically-acceptable buffer, such as phosphate-buffered saline, Ringer's solution, or dextrose solution. It can also contain other materials useful to the end-user, including other buffers, diluents, filters, needles, and syringes. The kit can also comprise a second or third container with another active agent, for example an antibiotic.

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The kit can also comprise a package insert containing written instructions for methods of inducing immunity against S agalactiae andor S. pyogenes and/or S pneumoniae or for treating S agalactiae andor S. pyogenes and/or S pneumoniae infections. The package insert can be an unapproved draft package insert or can be a package insert approved by the Food and Drug Administration (FDA) or other regulatory body.

The invention also provides a delivery device pre-filled with the immunogenic compositions of the invention.

The invention also provides a method for raising an immune response in a mammal comprising the step of administering an effective amount of a composition of the invention. The immune response is preferably protective and preferably involves antibodies and/or cell-mediated immunity. This immune response will preferably induce long lasting (e.g., neutralising) antibodies and a cell mediated immunity that can quickly respond upon exposure to one or more GBS and/or GAS and/or S. pneumoniae antigens. The method may raise a booster response.

The invention provides a method of neutralizing GBS, GAS, or *S. pneumoniae* infection in a mammal comprising the step of administering to the mammal an effective amount of the immunogenic compositions of the invention, a vaccine of the invention, or antibodies which recognize an immunogenic composition of the invention.

The mammal is preferably a human. Where the vaccine is for prophylactic use, the human is preferably a female (either of child bearing age or a teenager). Alternatively, the human may be elderly (e.g., over the age of 50, 55, 60, 65, 70 or 75) and may have an underlying disease such as diabetes or cancer. Where the vaccine is for therapeutic use, the human is preferably a pregnant female or an elderly adult.

These uses and methods are preferably for the prevention and/or treatment of a disease caused by *Streptococcus agalactiae*, or *S. pyogenes*, or *S. pneumoniae*. The compositions may also be

effective against other streptococcal bacteria. The compositions may also be effective against other Gram positive bacteria.

One way of checking efficacy of therapeutic treatment involves monitoring Gram positive bacterial infection after administration of the composition of the invention. One way of checking efficacy of prophylactic treatment involves monitoring immune responses against the Gram positive bacterial antigens in the compositions of the invention after administration of the composition.

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One way of checking efficacy of therapeutic treatment involves monitoring GBS infection after administration of the composition of the invention. One way of checking efficacy of prophylactic treatment involves monitoring immune responses against the GBS antigens in the compositions of the invention after administration of the composition.

A way of assessing the immunogenicity of the component proteins of the immunogenic compositions of the present invention is to express the proteins recombinantly and to screen patient sera or mucosal secretions by immunoblot. A positive reaction between the protein and the patient serum indicates that the patient has previously mounted an immune response to the protein in question- that is, the protein is an immunogen. This method may also be used to identify immunodominant proteins and/or epitopes.

Another way of checking efficacy of therapeutic treatment involves monitoring GBS or GAS or *S pneumoniae* infection after administration of the compositions of the invention. One way of checking efficacy of prophylactic treatment involves monitoring immune responses both systemically (such as monitoring the level of IgG1 and IgG2a production) and mucosally (such as monitoring the level of IgA production) against the GBS and/or GAS and/or *S pneumoniae* antigens in the compositions of the invention after administration of the composition. Typically, GBS and/or GAS and/or S pneumoniae serum specific antibody responses are determined post-immunization but prechallenge whereas mucosal GBS and/or GAS and/or *S pneumoniae* specific antibody body responses are determined post-immunization and post-challenge.

The vaccine compositions of the present invention can be evaluated in *in vitro* and *in vivo* animal models prior to host, *e.g.*, human, administration.

The efficacy of immunogenic compositions of the invention can also be determined in vivo by challenging animal models of GBS and/or GAS and/or S pneumoniae infection, e.g., guinea pigs or mice, with the immunogenic compositions. The immunogenic compositions may or may not be derived from the same serotypes as the challenge serotypes. Preferably the immunogenic compositions are derivable from the same serotypes as the challenge serotypes. More preferably, the immunogenic composition and/or the challenge serotypes are derivable from the group of GBS and/or GAS and/or S pneumoniae serotypes.

In vivo efficacy models include but are not limited to: (i) A murine infection model using human GBS and/or GAS and/or S pneumoniae serotypes; (ii) a murine disease model which is a murine model using a mouse-adapted GBS and/or GAS and/or S pneumoniae strain, such as those

strains outlined above which is particularly virulent in mice and (iii) a primate model using human GBS or GAS or S pneumoniae isolates.

The immune response may be one or both of a TH1 immune response and a TH2 response.

The immune response may be an improved or an enhanced or an altered immune response.

The immune response may be one or both of a systemic and a mucosal immune response.

Preferably the immune response is an enhanced system and/or mucosal response.

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An enhanced systemic and/or mucosal immunity is reflected in an enhanced TH1 and/or TH2 immune response. Preferably, the enhanced immune response includes an increase in the production of IgG1 and/or IgG2a and/or IgA

Preferably the mucosal immune response is a TH2 immune response. Preferably, the mucosal immune response includes an increase in the production of IgA.

Activated TH2 cells enhance antibody production and are therefore of value in responding to extracellular infections. Activated TH2 cells may secrete one or more of IL-4, IL-5, IL-6, and IL-10. A TH2 immune response may result in the production of IgG1, IgE, IgA and memory B cells for future protection.

A TH2 immune response may include one or more of an increase in one or more of the cytokines associated with a TH2 immune response (such as IL-4, IL-5, IL-6 and IL-10), or an increase in the production of IgG1, IgE, IgA and memory B cells. Preferably, the enhanced TH2 immune resonse will include an increase in IgG1 production.

A TH1 immune response may include one or more of an increase in CTLs, an increase in one or more of the cytokines associated with a TH1 immune response (such as IL-2, IFN γ , and TNF β), an increase in activated macrophages, an increase in NK activity, or an increase in the production of IgG2a. Preferably, the enhanced TH1 immune response will include an increase in IgG2a production.

Immunogenic compositions of the invention, in particular, immunogenic composition comprising one or more GAS antigens of the present invention may be used either alone or in combination with other GAS antigens optionally with an immunoregulatory agent capable of eliciting a Th1 and/or Th2 response.

Compositions of the invention will generally be administered directly to a patient. Certain routes may be favored for certain compositons, as resulting in the generation of a more effective immune response, preferably a CMI response, or as being less likely to induce side effects, or as being easier for administration. Direct delivery may be accomplished by parenteral injection (e.g. subcutaneously, intraperitoneally, intradermally, intravenously, intramuscularly, or to the interstitial space of a tissue), or by rectal, oral (e.g. tablet, spray), vaginal, topical, transdermal (e.g. see WO 99/27961) or transcutaneous (e.g. see WO 02/074244 and WO 02/064162), intranasal (e.g. see WO03/028760), ocular, aural, pulmonary or other mucosal administration.

The invention may be used to elicit systemic and/or mucosal immunity.

In one particularly preferred embodiment, the immunogenic composition comprises one or more GBS or GAS or S pneumoniae antigen(s) which elicits a neutralising antibody response and one or more GBS or GAS or S pneumoniae antigen(s) which elicit a cell mediated immune response. In this way, the neutralising antibody response prevents or inhibits an initial GBS or GAS or S pneumoniae infection while the cell-mediated immune response capable of eliciting an enhanced Th1 cellular response prevents further spreading of the GBS or GAS or S pneumoniae infection.

Preferably, the immunogenic composition comprises one or more GBS or GAS or S pneumoniae surface antigens and one or more GBS or GAS or S pneumoniae cytoplasmic antigens. Preferably the immunogenic composition comprises one or more GBS or GAS or S pneumoniae surface antigens or the like and one or other antigens, such as a cytoplasmic antigen capable of eliciting a Th1 cellular response.

Dosage treatment can be a single dose schedule or a multiple dose schedule. Multiple doses may be used in a primary immunisation schedule and/or in a booster immunisation schedule. In a multiple dose schedule the various doses may be given by the same or different routes *e.g.* a parenteral prime and mucosal boost, a mucosal prime and parenteral boost, *etc.*

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The compositions of the invention may be prepared in various forms. For example, the compositions may be prepared as injectables, either as liquid solutions or suspensions. Solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection can also be prepared (e.g. a lyophilised composition). The composition may be prepared for topical administration e.g. as an ointment, cream or powder. The composition may be prepared for oral administration e.g. as a tablet or capsule, as a spray, or as a syrup (optionally flavoured). The composition may be prepared for pulmonary administration e.g. as an inhaler, using a fine powder or a spray. The composition may be prepared as a suppository or pessary. The composition may be prepared for nasal, aural or ocular administration e.g. as drops. The composition may be in kit form, designed such that a combined composition is reconstituted just prior to administration to a patient. Such kits may comprise one or more antigens in liquid form and one or more lyophilised antigens.

Immunogenic compositions used as vaccines comprise an immunologically effective amount of antigen(s), as well as any other components, such as antibiotics, as needed. By 'immunologically effective amount', it is meant that the administration of that amount to an individual, either in a single dose or as part of a series, is effective for treatment or prevention, or increases a measurable immune response or prevents or reduces a clinical symptom. This amount varies depending upon the health and physical condition of the individual to be treated, age, the taxonomic group of individual to be treated (e.g. non-human primate, primate, etc.), the capacity of the individual's immune system to synthesise antibodies, the degree of protection desired, the formulation of the vaccine, the treating doctor's assessment of the medical situation, and other relevant factors. It is expected that the amount will fall in a relatively broad range that can be determined through routine trials.

Further Components of the Composition

The composition of the invention will typically, in addition to the components mentioned above, comprise one or more 'pharmaceutically acceptable carriers', which include any carrier that does not itself induce the production of antibodies harmful to the individual receiving the composition. Suitable carriers are typically large, slowly metabolised macromolecules such as proteins, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers, and lipid aggregates (such as oil droplets or liposomes). Such carriers are well known to those of ordinary skill in the art. The vaccines may also contain diluents, such as water, saline, glycerol, *etc.* Additionally, auxiliary substances, such as wetting or emulsifying agents, pH buffering substances, and the like, may be present. A thorough discussion of pharmaceutically acceptable excipients is available in Gennaro (2000) *Remington: The Science and Practice of Pharmacy.* 20th ed., ISBN: 0683306472.

Adjuvants

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Vaccines of the invention may be administered in conjunction with other immunoregulatory agents. In particular, compositions will usually include an adjuvant. Adjuvants for use with the invention include, but are not limited to, one or more of the following set forth below:

A. Mineral Containing Compositions

Mineral containing compositions suitable for use as adjuvants in the invention include mineral salts, such as aluminum salts and calcium salts. The invention includes mineral salts such as hydroxides (e.g. oxyhydroxides), phosphates (e.g. hydroxyphosphates, orthophosphates), sulfates, etc. (e.g. see chapters 8 & 9 of Vaccine Design... (1995) eds. Powell & Newman. ISBN: 030644867X. Plenum.), or mixtures of different mineral compounds (e.g. a mixture of a phosphate and a hydroxide adjuvant, optionally with an excess of the phosphate), with the compounds taking any suitable form (e.g. gel, crystalline, amorphous, etc.), and with adsorption to the salt(s) being preferred. The mineral containing compositions may also be formulated as a particle of metal salt (WO 00/23105).

Aluminum salts may be included in vaccines of the invention such that the dose of Al³⁺ is between 0.2 and 1.0 mg per dose.

B. Oil-Emulsions

Oil-emulsion compositions suitable for use as adjuvants in the invention include squalene-water emulsions, such as MF59 (5% Squalene, 0.5% Tween 80, and 0.5% Span 85, formulated into submicron particles using a microfluidizer). See WO90/14837. See also, Podda, "The adjuvanted influenza vaccines with novel adjuvants: experience with the MF59-adjuvanted vaccine", Vaccine (2001) 19: 2673-2680; Frey et al., "Comparison of the safety, tolerability, and immunogenicity of a MF59-adjuvanted influenza vaccine and a non-adjuvanted influenza vaccine in non-elderly adults", Vaccine (2003) 21:4234-4237. MF59 is used as the adjuvant in the FLUADTM influenza virus trivalent subunit vaccine.

Particularly preferred adjuvants for use in the compositions are submicron oil-in-water emulsions. Preferred submicron oil-in-water emulsions for use herein are squalene/water emulsions optionally containing varying amounts of MTP-PE, such as a submicron oil-in-water emulsion containing 4-5% w/v squalene, 0.25-1.0% w/v Tween 80 ™ (polyoxyelthylenesorbitan monooleate), and/or 0.25-1.0% Span 85™ (sorbitan trioleate), and, optionally, N-acetylmuramyl-L-alanyl-Disogluatminyl-L-alanine-2-(1'-2'-dipalmitoyl-sn-glycero-3-huydroxyphosphophoryloxy)-ethylamine (MTP-PE), for example, the submicron oil-in-water emulsion known as "MF59" (International Publication No. WO 90/14837; US Patent Nos. 6,299,884 and 6,451,325, incorporated herein by reference in their entireties; and Ott et al., "MF59 -- Design and Evaluation of a Safe and Potent Adjuvant for Human Vaccines" in Vaccine Design: The Subunit and Adjuvant Approach (Powell, M.F. and Newman, M.J. eds.) Plenum Press, New York, 1995, pp. 277-296). MF59 contains 4-5% w/v Squalene (e.g. 4.3%), 0.25-0.5% w/v Tween 80™, and 0.5% w/v Span 85™ and optionally contains various amounts of MTP-PE, formulated into submicron particles using a microfluidizer such as Model 110Y microfluidizer (Microfluidics, Newton, MA). For example, MTP-PE may be present in an amount of about 0-500 µg/dose, more preferably 0-250 µg/dose and most preferably, 0-100 μg/dose. As used herein, the term "MF59-0" refers to the above submicron oil-in-water emulsion lacking MTP-PE, while the term MF59-MTP denotes a formulation that contains MTP-PE. For instance, "MF59-100" contains 100 µg MTP-PE per dose, and so on. MF69, another submicron oil-inwater emulsion for use herein, contains 4.3% w/v squalene, 0.25% w/v Tween 80™, and 0.75% w/v Span 85™ and optionally MTP-PE. Yet another submicron oil-in-water emulsion is MF75, also known as SAF, containing 10% squalene, 0.4% Tween 80™, 5% pluronic-blocked polymer L121, and thr-MDP, also microfluidized into a submicron emulsion. MF75-MTP denotes an MF75 formulation that includes MTP, such as from 100-400 µg MTP-PE per dose.

Submicron oil-in-water emulsions, methods of making the same and immunostimulating agents, such as muramyl peptides, for use in the compositions, are described in detail in International Publication No. WO 90/14837 and US Patent Nos. 6,299,884 and 6,45 1,325, incorporated herein by reference in their entireties.

Complete Freund's adjuvant (CFA) and incomplete Freund's adjuvant (IFA) may also be used as adjuvants in the invention.

C. Saponin Formulations

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Saponin formulations, may also be used as adjuvants in the invention. Saponins are a heterologous group of sterol glycosides and triterpenoid glycosides that are found in the bark, leaves, stems, roots and even flowers of a wide range of plant species. Saponin from the bark of the Quillaia saponaria Molina tree have been widely studied as adjuvants. Saponin can also be commercially obtained from Smilax ornata (sarsaprilla), Gypsophilla paniculata (brides veil), and Saponaria officianalis (soap root). Saponin adjuvant formulations include purified formulations, such as QS21, as well as lipid formulations, such as ISCOMs.

Saponin compositions have been purified using High Performance Thin Layer Chromatography (HP-LC) and Reversed Phase High Performance Liquid Chromatography (RP-HPLC). Specific purified fractions using these techniques have been identified, including QS7, QS17, QS18, QS21, QH-A, QH-B and QH-C. Preferably, the saponin is QS21. A method of production of QS21 is disclosed in US Patent No. 5,057,540. Saponin formulations may also comprise a sterol, such as cholesterol (see WO96/33739).

Combinations of saponins and cholesterols can be used to form unique particles called Immunostimulating Complexs (ISCOMs). ISCOMs typically also include a phospholipid such as phosphatidylethanolamine or phosphatidyletholine. Any known saponin can be used in ISCOMs. Preferably, the ISCOM includes one or more of Quil A, QHA and QHC. ISCOMs are further described in EP0109942, WO 96/11711 and WO 96/33739. Optionally, the ISCOMS may be devoid of additional detergent. See WO 00/07621.

A review of the development of saponin based adjuvants can be found at Barr, et al., "ISCOMs and other saponin based adjuvants", Advanced Drug Delivery Reviews (1998) 32:247-271. See also Sjolander, et al., "Uptake and adjuvant activity of orally delivered saponin and ISCOM vaccines", Advanced Drug Delivery Reviews (1998) 32:321-338.

D. Virosomes and Virus Like Particles (VLPs)

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Virosomes and Virus Like Particles (VLPs) can also be used as adjuvants in the invention. These structures generally contain one or more proteins from a virus optionally combined or 20 formulated with a phospholipid. They are generally non-pathogenic, non-replicating and generally do not contain any of the native viral genome. The viral proteins may be recombinantly produced or isolated from whole viruses. These viral proteins suitable for use in virosomes or VLPs include proteins derived from influenza virus (such as HA or NA), Hepatitis B virus (such as core or capsid proteins), Hepatitis E virus, measles virus, Sindbis virus, Rotavirus, Foot-and-Mouth Disease virus, 25 Retrovirus, Norwalk virus, human Papilloma virus, HIV, RNA-phages, Qß-phage (such as coat proteins), GA-phage, fr-phage, AP205 phage, and Ty (such as retrotransposon Ty protein p1). VLPs are discussed further in WO 03/024480, WO 03/024481, and Niikura et al., "Chimeric Recombinant Hepatitis E Virus-Like Particles as an Oral Vaccine Vehicle Presenting Foreign Epitopes", Virology (2002) 293:273-280; Lenz et al., "Papillomarivurs-Like Particles Induce Acute Activation of 30 Dendritic Cells", Journal of Immunology (2001) 5246-5355; Pinto, et al., "Cellular Immune Responses to Human Papillomavirus (HPV)-16 L1 Healthy Volunteers Immunized with Recombinant HPV-16 L1 Virus-Like Particles", Journal of Infectious Diseases (2003) 188:327-338; and Gerber et al., "Human Papillomavrisu Virus-Like Particles Are Efficient Oral Immunogens when Coadministered with Escherichia coli Heat-Labile Entertoxin Mutant R192G or CpG", Journal of 35 Virology (2001) 75(10):4752-4760. Virosomes are discussed further in, for example, Gluck et al., "New Technology Platforms in the Development of Vaccines for the Future", Vaccine (2002) 20:B10 -B16. Immunopotentiating reconstituted influenza virosomes (IRIV) are used as the subunit antigen

WO 2006/078318

delivery system in the intranasal trivalent INFLEXAL™ product {Mischler & Metcalfe (2002) Vaccine 20 Suppl 5:B17-23} and the INFLUVAC PLUS™ product. PCT/US2005/027239

Е. Bacterial or Microbial Derivatives

Adjuvants suitable for use in the invention include bacterial or microbial derivatives such as:

(1) Non-toxic derivatives of enterobacterial lipopolysaccharide (LPS)

Such derivatives include Monophosphoryl lipid A (MPL) and 3-O-deacylated MPL (3dMPL). 3dMPL is a mixture of 3 De-O-acylated monophosphoryl lipid A with 4, 5 or 6 acylated chains. A preferred "small particle" form of 3 De-O-acylated monophosphoryl lipid A is disclosed in EP 0 689 454. Such "small particles" of 3dMPL are small enough to be sterile filtered through a 0.22 micron membrane (see EP 0 689 454). Other non-toxic LPS derivatives include monophosphoryl lipid A mimics, such as aminoalkyl glucosaminide phosphate derivatives e.g. RC-529. See Johnson et al. (1999) Bioorg Med Chem Lett 9:2273-2278.

(2) Lipid A Derivatives

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Lipid A derivatives include derivatives of lipid A from Escherichia coli such as OM-174. OM-174 is described for example in Meraldi et al., "OM-174, a New Adjuvant with a Potential for Human Use, Induces a Protective Response with Administered with the Synthetic C-Terminal Fragment 242-310 from the circumsporozoite protein of Plasmodium berghei", Vaccine (2003) 21:2485-2491; and Pajak, et al., "The Adjuvant OM-174 induces both the migration and maturation of murine dendritic cells in vivo", Vaccine (2003) 21:836-842.

(3) Immunostimulatory oligonucleotides

Immunostimulatory oligonucleotides suitable for use as adjuvants in the invention include nucleotide sequences containing a CpG motif (a sequence containing an unmethylated cytosine followed by guanosine and linked by a phosphate bond). Bacterial double stranded RNA or oligonucleotides containing palindromic or poly(dG) sequences have also been shown to be immunostimulatory.

The CpG's can include nucleotide modifications/analogs such as phosphorothioate modifications and can be double-stranded or single-stranded. Optionally, the guanosine may be replaced with an analog such as 2'-deoxy-7-deazaguanosine. See Kandimalla, et al., "Divergent synthetic nucleotide motif recognition pattern: design and development of potent immunomodulatory oligodeoxyribonucleotide agents with distinct cytokine induction profiles", Nucleic Acids Research (2003) 31(9): 2393-2400; WO02/26757 and WO99/62923 for examples of possible analog substitutions. The adjuvant effect of CpG oligonucleotides is further discussed in Krieg, "CpG motifs: the active ingredient in bacterial extracts?", Nature Medicine (2003) 9(7): 831-835; McCluskie, et al., "Parenteral and mucosal prime-boost immunization strategies in mice with hepatitis B surface antigen and CpG DNA", FEMS Immunology and Medical Microbiology (2002) 32:179-185; WO98/40100; US Patent No. 6,207,646; US Patent No. 6,239,116 and US Patent No. 6,429,199.

The CpG sequence may be directed to TLR9, such as the motif GTCGTT or TTCGTT. See Kandimalla, et al., "Toll-like receptor 9: modulation of recognition and cytokine induction by novel -240-

synthetic CpG DNAs" Biochemical Society Transactions (2003) 31 (part 3): 654-658. The CpG sequence may be specific for inducing a Th1 immune response, such as a CpG-A ODN, or it may be more specific for inducing a B cell response, such a CpG-B ODN. CpG-A and CpG-B ODNs are discussed in Blackwell, et al., "CpG-A-Induced Monocyte IFN-gamma-Inducible Protein-10 Production is Regulated by Plasmacytoid Dendritic Cell Derived IFN-alpha", J. Immunol. (2003) 170(8):4061-4068; Krieg, "From A to Z on CpG", TRENDS in Immunology (2002) 23(2): 64-65 and WO01/95935. Preferably, the CpG is a CpG-A ODN.

Preferably, the CpG oligonucleotide is constructed so that the 5' end is accessible for receptor recognition. Optionally, two CpG oligonucleotide sequences may be attached at their 3' ends to form "immunomers". See, for example, Kandimalla, et al., "Secondary structures in CpG oligonucleotides affect immunostimulatory activity", BBRC (2003) 306:948-953; Kandimalla, et al., "Toll-like receptor 9: modulation of recognition and cytokine induction by novel synthetic GpG DNAs", Biochemical Society Transactions (2003) 31(part 3):664-658; Bhagat et al., "CpG penta- and hexadeoxyribonucleotides as potent immunomodulatory agents" BBRC (2003) 300:853-861 and WO 03/035836.

(4) ADP-ribosylating toxins and detoxified derivatives thereof.

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Bacterial ADP-ribosylating toxins and detoxified derivatives thereof may be used as adjuvants in the invention. Preferably, the protein is derived from E. coli (i.e., E. coli heat labile enterotoxin "LT), cholera ("CT"), or pertussis ("PT"). The use of detoxified ADP-ribosylating toxins 20 as mucosal adjuvants is described in WO95/17211 and as parenteral adjuvants in WO98/42375. Preferably, the adjuvant is a detoxified LT mutant such as LT-K63, LT-R72, and LTR192G. The use of ADP-ribosylating toxins and detoxified derivaties thereof, particularly LT-K63 and LT-R72, as adjuvants can be found in the following references, each of which is specifically incorporated by reference herein in their entirety: Beignon, et al., "The LTR72 Mutant of Heat-Labile Enterotoxin of 25 Escherichia coli Enahnces the Ability of Peptide Antigens to Elicit CD4+ T Cells and Secrete Gamma Interferon after Coapplication onto Bare Skin", Infection and Immunity (2002) 70(6):3012-3019; Pizza, et al., "Mucosal vaccines: non toxic derivatives of LT and CT as mucosal adjuvants", Vaccine (2001) 19:2534-2541; Pizza, et al., "LTK63 and LTR72, two mucosal adjuvants ready for clinical trials" Int. J. Med. Microbiol (2000) 290(4-5):455-461; Scharton-Kersten et al., "Transcutaneous 30 Immunization with Bacterial ADP-Ribosylating Exotoxins, Subunits and Unrelated Adjuvants", Infection and Immunity (2000) 68(9):5306-5313; Ryan et al., "Mutants of Escherichia coli Heat-Labile Toxin Act as Effective Mucosal Adjuvants for Nasal Delivery of an Acellular Pertussis Vaccine: Differential Effects of the Nontoxic AB Complex and Enzyme Activity on Th1 and Th2 Cells" Infection and Immunity (1999) 67(12):6270-6280; Partidos et al., "Heat-labile enterotoxin of 35 Escherichia coli and its site-directed mutant LTK63 enhance the proliferative and cytotoxic T-cell responses to intranasally co-immunized synthetic peptides", Immunol. Lett. (1999) 67(3):209-216; Peppoloni et al., "Mutants of the Escherichia coli heat-labile enterotoxin as safe and strong adjuvants for intranasal delivery of vaccines", Vaccines (2003) 2(2):285-293; and Pine et al., (2002) "Intranasal -241-

immunization with influenza yaccine and a detoxified mutant of heat labile enterotoxin from Escherichia coli (LTK63)" J. Control Release (2002) 85(1-3):263-270. Numerical reference for amino acid substitutions is preferably based on the alignments of the A and B subunits of ADP-ribosylating toxins set forth in Domenighini et al., Mol. Microbiol (1995) 15(6):1165-1167, specifically incorporated herein by reference in its entirety.

F. Bioadhesives and Mucoadhesives

Bioadhesives and mucoadhesives may also be used as adjuvants in the invention. Suitable bioadhesives include esterified hyaluronic acid microspheres (Singh *et al.* (2001) *J. Cont. Rele.* 70:267-276) or mucoadhesives such as cross-linked derivatives of poly(acrylic acid), polyvinyl alcohol, polyvinyl pyrollidone, polysaccharides and carboxymethylcellulose. Chitosan and derivatives thereof may also be used as adjuvants in the invention. E.g. WO99/27960.

G. Microparticles

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Microparticles may also be used as adjuvants in the invention. Microparticles (*i.e.* a particle of ~100nm to ~150 μ m in diameter, more preferably ~200nm to ~30 μ m in diameter, and most preferably ~500nm to ~10 μ m in diameter) formed from materials that are biodegradable and non-toxic (*e.g.* a poly(α -hydroxy acid), a polyhydroxybutyric acid, a polyorthoester, a polyanhydride, a polycaprolactone, *etc.*), with poly(lactide-co-glycolide) are preferred, optionally treated to have a negatively-charged surface (*e.g.* with SDS) or a positively-charged surface (*e.g.* with a cationic detergent, such as CTAB).

H. Liposomes

Examples of liposome formulations suitable for use as adjuvants are described in US Patent No. 6,090,406, US Patent No. 5,916,588, and EP 0 626 169.

I. Polyoxyethylene ether and Polyoxyethylene Ester Formulations

Adjuvants suitable for use in the invention include polyoxyethylene ethers and polyoxyethylene esters. WO99/52549. Such formulations further include polyoxyethylene sorbitan ester surfactants in combination with an octoxynol (WO01/21207) as well as polyoxyethylene alkyl ethers or ester surfactants in combination with at least one additional non-ionic surfactant such as an octoxynol (WO 01/21152).

Preferred polyoxyethylene ethers are selected from the following group: polyoxyethylene-9-lauryl ether (laureth 9), polyoxyethylene-9-steoryl ether, polyoxytheylene-8-steoryl ether, polyoxyethylene-4-lauryl ether, polyoxyethylene-35-lauryl ether, and polyoxyethylene-23-lauryl ether.

J. Polyphosphazene (PCPP)

PCPP formulations are described, for example, in Andrianov et al., "Preparation of hydrogel microspheres by coacervation of aqueous polyphophazene solutions", Biomaterials (1998) 19(1-3):109-115 and Payne et al., "Protein Release from Polyphosphazene Matrices", Adv. Drug. Delivery Review (1998) 31(3):185-196.

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Examples of muramyl peptides suitable for use as adjuvants in the invention include N-acetyl-muramyl-L-threonyl-D-isoglutamine (thr-MDP), N-acetyl-normuramyl-l-alanyl-d-isoglutamine (nor-MDP), and N-acetylmuramyl-l-alanyl-d-isoglutaminyl-l-alanine-2-(1'-2'-dipalmitoyl-sn-glycero-3-hydroxyphosphoryloxy)-ethylamine MTP-PE).

L. Imidazoquinolone Compounds.

Examples of imidazoquinolone compounds suitable for use adjuvants in the invention include Imiquamod and its homologues, described further in Stanley, "Imiquimod and the imidazoquinolones: mechanism of action and therapeutic potential" Clin Exp Dermatol (2002) <u>27(7):571-577</u> and Jones, "Resiguimod 3M", Curr Opin Investig Drugs (2003) 4(2):214-218.

The invention may also comprise combinations of aspects of one or more of the adjuvants identified above. For example, the following adjuvant compositions may be used in the invention:

- (1) a saponin and an oil-in-water emulsion (WO 99/11241);
- (2) a saponin (e.g., QS21) + a non-toxic LPS derivative (e.g. 3dMPL) (see WO 94/00153);
- 15 (3) a saponin (e.g., QS21) + a non-toxic LPS derivative (e.g. 3dMPL) + a cholesterol;
 - (4) a saponin (e.g. QS21) + 3dMPL + IL-12 (optionally + a sterol) (WO 98/57659);
 - (5) combinations of 3dMPL with, for example, QS21 and/or oil-in-water emulsions (See European patent applications 0835318, 0735898 and 0761231);
 - (6) SAF, containing 10% Squalane, 0.4% Tween 80, 5% pluronic-block polymer L121, and thr-MDP, either microfluidized into a submicron emulsion or vortexed to generate a larger particle size emulsion.
 - (7) RibiTM adjuvant system (RAS), (Ribi Immunochem) containing 2% Squalene, 0.2% Tween 80, and one or more bacterial cell wall components from the group consisting of monophosphorylipid A (MPL), trehalose dimycolate (TDM), and cell wall skeleton (CWS), preferably MPL + CWS (DetoxTM);
 - (8) one or more mineral salts (such as an aluminum salt) + a non-toxic derivative of LPS (such as 3dPML).
 - (9) one or more mineral salts (such as an aluminum salt) + an immunostimulatory oligonucleotide (such as a nucleotide sequence including a CpG motif). Combination No. (9) is a preferred adjuvant combination.

M. Human Immunomodulators .

Human immunomodulators suitable for use as adjuvants in the invention include cytokines, such as interleukins (e.g. IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-12, etc.), interferons (e.g. interferon-γ), macrophage colony stimulating factor, and tumor necrosis factor.

Aluminum salts and MF59 are preferred adjuvants for use with injectable influenza vaccines. Bacterial toxins and bioadhesives are preferred adjuvants for use with mucosally-delivered vaccines, such as nasal vaccines.

The immunogenic compositions of the present invention may be administed in combination with an antibiotic treatment regime. In one embodiment, the antibiotic is administered prior to administration of the antigen of the invention or the composition comprising the one or more of the antigens of the invention.

In another embodiment, the antibiotic is administered subsequent to the administration of the one or more antigens of the invention or the composition comprising the one or more antigens of the invention. Examples of antibiotics suitable for use in the treatment of the Steptococcal infections of the invention include but are not limited to penicillin or a derivative thereof or clindamycin or the like.

Further antigens

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The compositions of the invention may further comprise one or more additional Gram positive bacterial antigens which are not associated with an AI. Preferably, the Gram positive bacterial antigens that are not associated with an AI can provide protection across more than one serotype or strain isolate. For example, a first non-AI antigen, in which the first non-AI antigen is at least 90% (i.e., at least 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100%) homologous to the amino acid sequence of a second non-AI antigen, wherein the first and the second non-AI antigen are derived from the genomes of different serotypes of a Gram positive bacteria, may be further included in the compositions. The first non-AI antigen may also be homologous to the amino acid sequence of a third non-AI antigen, such that the first non-AI antigen, the second non-AI antigen, and the third non-AI antigen may also be homologous to the amino acid sequence of a fourth non-AI antigen, such that the first non-AI antigen may also be homologous to the amino acid sequence of a fourth non-AI antigen, such that the first non-AI antigen, the second non-AI antigen, and the fourth non-AI antigen are derived from the genomes of different serotypes of a Gram positive bacteria.

The first non-AI antigen may be GBS 322. The amino acid sequence of GBS 322 across GBS strains from serotypes Ia, Ib, II, III, V, and VIII is greater than 90%. Alternatively, the first non-AI antigen may be GBS 276. The amino acid sequence of GBS 276 across GBS strain from serotypes Ia, Ib, II, III, V, and VIII is greater than 90%. Table 13 provides the percent amino acid sequence identity of GBS 322 and GBS 276 across different GBS strains and serotypes.

Table 13.	Conservation of GBS 3	22 and GRS 276 amino	acid seguences
radio 15.	Consci vation of Obb 5.		acta sequettees

Serotype	Strains		GBS 322	GBS 276		
		cGH	%AA identity	сGH	%AA identity	
Ia	090	+	98.60	+	97.90	
	A909	+	98.30	+	97.90	
	515	+	98.80	+	97.50	
	DK1	+		+		
	DK8	+		+		
	Davis	+		+		
Ib	7357b	+		+		
	Н36В	+	98.30	+	97.80	
п	18RS21	+	100.00	+	99.90	
Γ	DK21	+		+		

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Serotype	Strains	ը ռուլ ուսը դրուլ, G	BS 322	(GBS 276
[m] [] ["cGH	%AA identity	cGH	%AA identity
Ш	NEM316	+	100.00	+-	97.00
	СОН31	+		+	
	D136	+		+	
	M732	+	98.00	+	100.00
	COH1	+	98.30	+	100.00
···	M781	+	98.30	+	99.60
No type	CJB110	+	98.60	+	97.90
	1169NT	+	97.40	+	97.90
\mathbf{v}	CJB111	+	100.00	+	
	2603	+	100.00	+	. 100.00
VIII	JM130013	+	100.00	+	97.90
	SMU014	+		+	
1	total		98.28+/-0.4	22/22	98.44 +/-1.094

As an example, inclusion of a non-AI protein, GBS 322, in combination with AI antigens GBS 67, GBS 80, and GBS 104 provided protection to newborn mice in an active maternal immunization assay.

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Table 14: Active maternal immunization assay for a combination of fragments from GBS 322, GBS 80, GBS 104, and GBS 67

		FA	C5 (A A	Nean) 👉	MIX=322+	80+104+67	PE PE	
GBS strains	Туре	GBS 80	GBS 67	<i>G</i> B5 322	alive/treated	% protection	alive/treated	1
515	Ια	0	409	227	39/40	97	6/40	15
7357b-	Ιb	91	316	102	19/30	63	1/30	3
DK21	п	0	331	416	25/34	73	17/48	35
5401	11	170	618	135	35/40	87	3/37	8
3050	II	43	460	188	48/48	100	1/30	3
COH1	III	305	0	130	36/36	100	7/40	17
M781	III	65	0	224	30/40	75	4/39	10
2603	٧	125	105	313	27/33	82	10/35	28
CJB111	٧	370	481	63	25/28	89	4/46	9
JM9130013	VIII	597	83	143	37/39	95	5/40	12
JMU071	VIII	556	79	170	44/50	88	18/50	36
NT1169	NT	0	443	213	12/32	37	11/35	31

In fact, the non-AI GBS 322 antigen may itself provide protection to newborn mice in an active maternal immunization assay.

Table 16: Active maternal immunization assay for

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	lav.	LC	ΙU);	Acuve	t ma	ternai	111111111111	uzauor	i assav	m	eacn	OT UEBS	ΛU	ลทด	GBS 322 ar	itioens

			<i>G</i> BS 80		<i>G</i> BS 322				
		FACS	Protection	(% survival)	FACS	Protection (% survival)		
GBS strains	Type	△ Mean	antigen	ctrl-	∆ Mean	antigen	ctrl-		
CJB111	· v	370	72 %	40%	63	57%	40%		
COH1	III	305	76 %	10%	130	3%	10%		
2603	V	82	22 %	34%	313	83 %	34%		
7357b-	Ib	91	36%	34%	102	43%	34%		
18RS21	II	0	15%	24%	268	84 %	24%		
DK21	II	0	10%	21%	416	67 %	25%		
A909	Ια	0	0%	14%		***************************************			
090	Ia	0	0%	0%	************************		 		
H36B	Тb			of , and i become committees specimentary. I appear of economical	105	34%	32%		

Thus, inclusion of a non-AI protein in an immunogenic composition of the invention may provide increased protection a mammal.

The immunogenic compositions comprising *S. pneumonaie* AI polypeptides may further secondary SP protein antigens which include (a) any of the SP protein antigens disclosed in WO 02/077021 or U.S. provisional application _______, filed April 20, 2005 (Attorney Docket Number 002441.00154), (2) immunogenic portions of the antigens comprising at least 7 contiguous amino acids, (3) proteins comprising amino acid sequences which retain immunogenicity and which are at least 95% identical to these SP protein antigens (*e.g.*, 95%, 96%, 97%, 98%, 99%, or 99.5% identical), and (4) fusion proteins, including hybrid SP protein antigens, comprising (1)-(3).

Alternatively, the invention may include an immunogenic composition comprising a first and a second Gram positive bacteria non-AI protein, wherein the polynucleotide sequence encoding the sequence of the first non-AI protein is less than 90% (i.e., less than 90, 88, 86, 84, 82, 81, 78, 76, 74, 72, 70, 65, 60, 55, 50, 45, 40, 35, or 30 percent) homologous than the corresponding sequence in the genome of the second non-AI protein.

The compositions of the invention may further comprise one or more additional non-Gram positive bacterial antigens, including additional bacterial, viral or parasitic antigens. The compositions of the invention may further comprise one or more additional non-GBS antigens, including additional bacterial, viral or parasitic antigens.

In another embodiment, the GBS antigen combinations of the invention are combined with one or more additional, non-GBS antigens suitable for use in a vaccine designed to protect elderly or immunocomprised individuals. For example, the GBS antigen combinations may be combined with an antigen derived from the group consisting of *Enterococcus faecalis*, *Staphylococcus aureus*, *Staphylococcus epidermis*, *Pseudomonas aeruginosa*, *Legionella pneumophila*, *Listeria monocytogenes*, *Neisseria meningitides*, influenza, and Parainfluenza virus ('PIV').

Where a saccharide or carbohydrate antigen is used, it is preferably conjugated to a carrier protein in order to enhance immunogenicity {e.g. Ramsay et al. (2001) Lancet 357(9251):195-196; Lindberg (1999) Vaccine 17 Suppl 2:S28-36; Buttery & Moxon (2000) JR Coll Physicians Lond 34:163-168; Ahmad & Chapnick (1999) Infect Dis Clin North Am 13:113-133, vii.; Goldblatt (1998) J. Med. Microbiol. 47:563-567; European patent 0 477 508; US Patent No. 5,306,492; International patent application WO98/42721; Conjugate Vaccines (eds. Cruse et al.) ISBN 3805549326, particularly vol. 10:48-114; and Hermanson (1996) Bioconjugate Techniques ISBN: 0123423368 or 012342335X}. Preferred carrier proteins are bacterial toxins or toxoids, such as diphtheria or tetanus toxoids. The CRM₁₉₇ diphtheria toxoid is particularly preferred {Research Disclosure, 453077 (Jan 2002)}. Other carrier polypeptides include the N.meningitidis outer membrane protein (EP-A-0372501), synthetic peptides (EP-A-0378881; EP-A-0427347), heat shock proteins (WO 93/17712; WO 94/03208), pertussis proteins (WO 98/58668; EP A 0471177), protein D from H.influenzae (WO 00/56360), cytokines (WO 91/01146), lymphokines, hormones, growth factors, toxin A or B from C.difficile (WO00/61761), iron-uptake proteins (WO01/72337), etc. Where a mixture comprises capsular saccharides from both serogroups A and C, it may be preferred that the ratio (w/w) of MenA saccharide: MenC saccharide is greater than 1 (e.g. 2:1, 3:1, 4:1, 5:1, 10:1 or higher). Different saccharides can be conjugated to the same or different type of carrier protein. Any suitable conjugation reaction can be used, with any suitable linker where necessary.

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Toxic protein antigens may be detoxified where necessary e.g. detoxification of pertussis toxin by chemical and/or genetic means.

Where a diphtheria antigen is included in the composition it is preferred also to include tetanus antigen and pertussis antigens. Similarly, where a tetanus antigen is included it is preferred also to include diphtheria and pertussis antigens. Similarly, where a pertussis antigen is included it is preferred also to include diphtheria and tetanus antigens.

Antigens in the composition will typically be present at a concentration of at least 1µg/ml each. In general, the concentration of any given antigen will be sufficient to elicit an immune response against that antigen.

As an alternative to using protein antigens in the composition of the invention, nucleic acid encoding the antigen may be used {e.g. refs. Robinson & Torres (1997) Seminars in Immunology 9:271-283; Donnelly et al. (1997) Annu Rev Immunol 15:617-648; Scott-Taylor & Dalgleish (2000) Expert Opin Investig Drugs 9:471-480; Apostolopoulos & Plebanski (2000) Curr Opin Mol Ther 2:441-447; Ilan (1999) Curr Opin Mol Ther 1:116-120; Dubensky et al. (2000) Mol Med 6:723-732; Robinson & Pertmer (2000) Adv Virus Res 55:1-74; Donnelly et al. (2000) Am J Respir Crit Care Med 162(4 Pt 2):S190-193; and Davis (1999) Mt. Sinai J. Med. 66:84-90}. Protein components of the compositions of the invention may thus be replaced by nucleic acid (preferably DNA e.g. in the form of a plasmid) that encodes the protein.

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Definitions
The term "comprising" means "including" as well as "consisting" e.g. a composition "comprising" X may consist exclusively of X or may include something additional e.g. X + Y.

The term "about" in relation to a numerical value x means, for example, $x\pm10\%$.

References to a percentage sequence identity between two amino acid sequences means that, when aligned, that percentage of amino acids are the same in comparing the two sequences. This alignment and the percent homology or sequence identity can be determined using software programs known in the art, for example those described in section 7.7.18 of Current Protocols in Molecular Biology (F.M. Ausubel et al., eds., 1987) Supplement 30. A preferred alignment is determined by the Smith-Waterman homology search algorithm using an affine gap search with a gap open penalty of 12 and a gap extension penalty of 2, BLOSUM matrix of 62. The Smith-Waterman homology search algorithm is disclosed in Smith & Waterman (1981) Adv. Appl. Math. 2: 482-489.

The invention is further illustrated, without limitation, by the following examples.

EXAMPLE 1: Binding of an Adhesin Island surface protein, GBS 80, to Fibrinogen and Fibronectin.

This example demonstrates that an Adhesin Island surface protein, GBS 80 can bind to fibrinogen and fibronectin.

An enzyme-linked immunosorbent assay (ELISA) was used to analyse the in vitro binding ability of recombinant GBS 80 to immobilized extra-cellular matrix (ECM) proteins but not to bovine serum albumin (BSA). Microtiter plates were coated with ECM proteins (fibrinogen, fibronectin, laminin, collagen type IV) and binding assessed by adding varying concentrations of a recombinant form of GBS 80, over-expressed and purified from E. coli (FIGURE 5A). Plates were then incubated sequentially with a) mouse anti-GBS 80 primary antibody; b) rabbit anti-mouse AP-conjugated secondary antibody; c) pNPP colorimetric substrate. Relative binding was measured by monitoring absorbance at 405 nm, using 595 nm as a reference wavelength. Figure 5b shows binding of recombinant GBS 80 to immobilized ECM proteins (1 µg) as a function of concentration of GBS 80. BSA was used as a negative control. Data points represent the means of OD_{405} values \pm standard deviation for 3 wells.

Binding of GBS 80 to the tested ECM proteins was found to be concentration dependent and exhibited saturation kinetics. As is also evident from FIGURE 5, binding of GBS 80 to fibronectin and fibrinogen was greater than binding to laminin and collagen type IV at all the concentrations tested.

EXAMPLE 2: GBS 80 is required for surface localization of GBS 104.

This example demonstrates that co-expression of GBS 80 is required for surface localization of GBS 104.

The polycistronic nature of the Adhesin Island I mRNA was investigated through reverse transcriptase-PCR (RT-PCR) analysis employing primers designed to detect transcripts arising from contiguous genes. Total RNA was isolated from GBS cultures grown to an optical density at 600 nm -248-

(OD₆₀₀) of 0.3 in THB (Todd-Hewitt broth) by the RNeasy Total RNA isolation method (Qiagen) according to the manufacturer's instructions. The absence of contaminating chromosomal DNA was confirmed by failure of the gene amplification reactions to generate a product detectable by agarose gel electrophoresis, in the absence of reverse transcriptase. RT-PCR analysis was performed with the Access RT-PCR system (Promega) according to the manufacturer's instructions, employing PCR cycling temperatures of 60°C for annealing and 70°C for extension. Amplification products were visualized alongside 100-bp DNA markers in 2% agarose gels after ethidium bromide staining.

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FIGURE 5 shows that all the genes are co-transcribed as an operon. A schematic of the AI-1 operon is shown above the agarose gel analysis of the RT-PCR products. Large rectangular arrows indicate the predicted transcript direction. Primer pairs were selected such as "1-4" cross the 3'finish-5'start of successive genes and overlap each gene by at least 200 bp. Additionally, "1" crosses a putative rho-independent transcriptional terminator. "5" is an internal GBS 80 control and "6" is an unrelated control from a highly expressed gene. Lanes: "a": RNA plus RTase enzyme; "b" RNA without RTase; "c": genomic DNA control.

In the effort to elucidate the functions of the AI-1 proteins, in frame deletions of all of the genes within the operon have been constructed and the resulting mutants characterized with respect to surface exposure of the encoded antigens (see FIGURE 8).

Each in-frame deletion mutation was constructed by splice overlap extension PCR (SOE-PCR) essentially as decribed by Horton et al. [Horton R, M., Z, L, Cai, S, N, Ho, L, R, Pease (1990) Biotechniques 8:528-35] using suitable primers and cloned into the temperature sensitive shuttle vector pJRS233 to replace the wild type copy by allelic exchange [Perez-Casal, J., J. A. Price, et al. (1993) Mol Microbiol 8(5): 809-19.]. All plasmid constructions utilized standard molecular biology techniques, and the identities of DNA fragments generated by PCR were verified by sequencing. Following SOE-PCR, the resulting mutant DNA fragments were digested with XhoI and EcoRI, and ligated into a similarly digested pJRS233. The resuting vectors were introduced by electroporation into the chromosome of 2603 and COH1 GBS strains in a three-step process, essentially as described in Framson et al. [Framson, P. E., A. Nittayajarn, J. Merry, P. Youngman, and C. E. Rubens. (1997) Appl. Environ. Microbiol. 63(9):3539-47]. Briefly, the vector pJRS233 contains an erm gene encoding erythromycin resistance and a temperature-sensitive gram-positive replicon that is active at 30°C but not at 37°C. Initially, the constructs are electroporated into GBS electro-competent cells prepared as described by Frameson et al., and transformants containing free plasmid are selected by their ability to grow at 30°C on Todd-Hewitt Broth (THB) agar plates containing 1 µg/ml erythromycin. The second step includes a selection step for strains in which the plasmid has integrated into the chromosome via a single recombination event over the homologous plasmid insert and chromosome sequence by their ability to grow at 37°C on THB agar medium containing 1 mg/ml erythromycin. In the third step, GBS cells containing the plasmid integrated within the chromosome (integrants) are serially passed in broth culture in the absence of antibiotics at 30°C. Plasmid excision

from the chromosome via a second recombination event over the duplicated target gene sequence either completed the allelic exchange or reconstituted the wild-type genotype. Subsequent loss of the plasmid in the absence of antibiotic selection pressure resulted in an erythromycin-sensitive phenotype. In order to assess gene replacement a screening of erythromycin-sensitive colonies was performed by analysis of the target gene PCR amplicons.

FIGURE 7 reports a schematic of the IS-1 operon for each knock-out strain generated, along with the deletion position within the amino acidic sequence. Most data presented here concern the COH1 deletion strains, in which the expression of each of the antigens is higher by DNA microarray analysis (data not shown) as well as detectable by FACS analysis (see FIGURE 8). The double mutant in 2603 Δ 80, Δ 104 double mutant was constructed by sequential allelic exchanges of the shown alleles.

Immunization protocol

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Immune sera for FACS experiments were obtained as follows.

Groups of 4 CD-1 outbred female mice 6-7 weeks old (Charles River Laboratories, Calco Italy) were immunized with the selected GBS antigens, (20 µg of each recombinant GBS antigen), suspended in 100 µl of PBS. Each group received 3 doses at days 0, 21 and 35. Immunization was performed through intra-peritoneal injection of the protein with an equal volume of Complete Freund's Adjuvant (CFA) for the first dose and Incomplete Freund's Adjuvant (IFA) for the following two doses. In each immunization scheme negative and positive control groups are used. Immune response was monitored by using serum samples taken on day 0 and 49.

FACS analysis

Preparation of paraformaldehyde treated GBS cells and their FACS analysis were carried out as follows.

GBS serotype COH1 strain cells were grown in Todd Hewitt Broth (THB; Difco Laboratories, Detroit, Mich.) to OD600nm = 0.5. The culture was centrifuged for 20 minutes at 5000 rpm and bacteria were washed once with PBS, resuspended in PBS containing 0.05% paraformaldehyde, and incubated for 1 hours at 37 °C and then overnight at 4°C. 50µl of fixed bacteria (OD600 0.1) were washed once with PBS, resuspended in 20µl of Newborn Calf Serum, (Sigma) and incubated for 20 min. at room temperature. The cells were then incubated for 1 hour at 4°C in 100µl of preimmune or immune sera, diluted 1:200 in dilution buffer (PBS, 20% Newborn Calf Serum, 0.1% BSA). After centrifugation and washing with 200µl of washing buffer (0.1% BSA in PBS), samples were incubated for 1 hour at 4°C with 50µl of R-Phicoerytrin conjugated F(ab)2 goat anti-mouse IgG (Jackson ImmunoResearch Laboratories; Inc.), diluted 1:100 in dilution buffer. Cells were washed with 200µl of washing buffer and resuspended in 200µl of PBS. Samples were analysed using a FACS Calibur apparatus (Becton Dickinson, Mountain View, Calf.) and data were analyzed using the Cell Quest Software (Becton Dickinson). A shift in mean fluorescence intensity of > 75 channels compared to preimmune sera from the same mice was considered positive. This cutoff

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Was determined from the mean plus two standard deviations of shifts obtained with control sera raised against mock purified recombinant proteins from cultures of *E. coli* carrying the empty expression vector and included in every experiment. Artifacts due to bacterial lysis were excluded using antisera raised against 6 different known cytoplasmic proteins all of which were negative

FACS data on COH1 single KO mutants for GBS 104 and GBS 80 indicated that GBS 80 is required for surface localization of GBS 104.

As shown in FIGURE 8, GBS 104 is not surface exposed in the Δ80 strain (second column, bottom), but is present in the whole protein extracts (see FIGURE 10). Mean shift values suggest that GBS 104 is partially responsible for GBS 80 surface exposure (Mean shift of GBS 80 is reduced to ~60% wild-type levels in Δ104), and that GBS 80 is over-expressed in the complemented strain (mean shift value ~200% wild-type level). The Δ80/pGBS 80 strain contains the GBS 80 orf cloned in the shuttle-vector pAM401 (Wirth, R., F. Y. An, et al. (1986). J Bacteriol 165(3): 831-6). The vector alone does not alter the secretion pattern of GBS 104 (right column). FACS was performed on midlog fixed bacteria with mouse polyclonal antibodies as indicated at left. Black peak is pre-immune sera, colored peaks are sera from immunized animals.

EXAMPLE 3: Deletion of GBS 80 causes attenuation in vivo.

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This example demonstrates that deletion of GBS 80 causes attenuation *in vivo*, suggesting that this protein contributes to bacterial virulence.

By using a mouse animal model, we studied the role of GBS 80 and GBS 104 in the virulence of S. agalactiae.

Groups of ten outbred female mice 5-6 week weeks old (Charles River Laboratories, Calco Italy) were inoculated intraperitoneally with different dilutions of the mutant strains and LD50 (lethal dose 50) were calculated according to the method of Reed and Muench [Reed, L. J. and H. Muench (1938). The American Journal of Hygiene 27(3): 493-7]. As presented in the table below the number of colony forming units (cfu) counted for both the $\Delta 80$ and the $\Delta 80$, $\Delta 104$ double mutants is about 10 fold higher when compared to the wild type strain suggesting that inactivation of GBS 80 but not GBS 104 is responsible for an attenuation in virulence. This finding indicates that GBS 80 gene in the AI-1 might contribute to virulence.

Table Lethal dose 50% analysis of AI-1 mutants in the 2603 strain background. LD50s were performed by IP injection of female CD1 mice at an age of 5-6 weeks. LD50s were calculated by the method of Reed and Muench (8).

GBS strain	LD ₅₀ , cfu	Number of Experiments
Wild Type 2603	2×10^{8}	4
Δ104 mutant	$\sim 2 \times 10^{8}$	1
Δ80 mutant	2.6×10^9	3
$\Delta 80$, $\Delta 104$ double mutant	$\sim 2 \times 10^9$	1

EXAMPLE 4: Effect of Adhesin Island Sortase Deletions on Surface Antigen Presentation

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This example demonstrates the effect of adhesin island sortase deletions on surface antigen presentation.

FACS analysis results set forth in FIGURE 9 show that a deletion in sortase SAG0648 prevented GBS 104 from reaching the surface and slightly reduced the surface exposure of GBS 80 (fourth panel; mean shift value ~60% wild-type COH1). In the double sortase knock-out strain, neither antigen was surface exposed (far right panel). Either sortase alone was sufficient for GBS 80 to arrive at the bacterial surface (third and fourth columns, top). No effect was seen on surface exposure of antigens GBS 80 or GBS 104 in the Δ GBS 52 strain. Antibodies derived from purified GBS 52 were either non-specific or were FACS negative for GBS 52 (data not shown). FACS analysis was performed as described above (see EXAMPLE 2).

As shown in FIGURE 10, inactivation of GBS 80 has no effect on GBS 104 expression as much as GBS 104 knock out doesn't change the total amount GBS 80 expressed. The Western blot of whole protein extracts (strains noted above lanes) probed with anti-GBS 80 antisera is shown in panel A. Arrow indicates expected size of GBS 80 (60 kDa). GBS 80 antibodies recognize a doublet, the lower band is not present in $\triangle GBS$ 80 strains. Panel B shows a Western blot of whole protein extracts probed with anti-GBS 104 antisera. Arrow indicates expected size of GBS 104 (99.4 kDa). Protein extracts were prepared from the same bacterial cultures used for FACS (FIGURES 8 and 9). In conclusion, although GBS 104 does not arrive at the surface in the Δ80 strain by FACS (FIGURE 8, second column), it is present at approximately wild-type levels in the whole protein preps (B, second lane). Approximately 20 µg of each protein extract was loaded per lane.

Western-blot analysis

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Aliquots of total protein extract mixed with SDS loading buffer (1x: 60 mM TRIS-HCl pH 6.8, 5% w/v SDS, 10% v/v glycerin, 0.1% Bromophenol Blue, 100 mM DTT) and boiled 5 minutes at 95° C, were loaded on a 12.5% SDS-PAGE precast gel (Biorad). The gel is run using a SDS-PAGE running buffer containing 250 mM TRIS, 2.5 mM Glycine and 0.1 %SDS. The gel is electroblotted onto nitrocellulose membrane at 200 mA for 60 minutes. The membrane is blocked for 60 minutes with PBS/0.05 % Tween-20 (Sigma), 10% skimmed milk powder and incubated O/N at 4° C with PBS/0.05 % Tween 20, 1% skimmed milk powder, with the appropriate dilution of the sera. After washing twice with PBS/0.05 % Tween, the membrane is incubated for 2 hours with peroxidaseconjugated secondary anti-mouse antibody (Amersham) diluted 1:4000. The nitrocellulose is washed three times for 10 minutes with PBS/0.05 % Tween and once with PBS and thereafter developed by Opti-4CN Substrate Kit (Biorad).

Example 5: Binding of Adhesin Island proteins to epithelial cells and effect of Adhesin Island proteins on capacity of GBS to adhere to epithelial cells.

This example illustrates the binding of AI proteins to epithelial cells and the effect of AI proteins on the capacity of GBS to adhere to epithelial cells.

Applicants analysed whether recombinant AI surface proteins GBS 80 or GBS 104 would demonstrate binding to various epithelial cells in a FACS analysis. Applicants also analysed whether -252WO 2006/078318

deletion of AI surface proteins GBS 80 or GBS 104 would effect the capacity of GBS to adhere to and invade ME180 cervical epithelial cells.

As shown in Figure 28, deletion of GBS 80 sequence from GBS strain isolate 2603 (serotype V) did not affect the capacity of the mutated GBS to adhere to and invade ME180 cervical epithelial cells. Here ME180 cervical carcinoma epithelial cells were infected with wild type GBS 2603 or GBS 2603 Δ80 isogenic mutant. After two hours of infection, non-adherent bacteria were washed off and infection prolonged for a further two hours and four hours. In invasion experiments, after each time point, was followed by a two hour antibiotic treatment. Cells were then lysed with 1% saponin and lysates plated on TSA plates. As shown in Figure 28, there was little difference between the percent invasion or percent adhesion of wild type and mutant strains up to the four hour time point.

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Figure 30 repeats this experiment with both $\Delta 104$ and $\Delta 80$ mutants from a different strain isolate. Here, ME180 cervical carcinoma epithelial cells were infected with GBS strain isolate COH (serotype III) wild type or COH1 ΔGBS 104 or COH1 $\Delta 80$ isogenic mutant. After one hour of infection, non-adherent bacteria were washed off and the cells were lysed with 1% saponin. The lysates were plated on TSA plates. As shown in Figure 30, while there was little difference in the percent invasion, there was a significant decrease in the percent association of the $\Delta 104$ mutant compared to both the wild type and $\Delta 80$ mutant.

The affect of AI surface proteins on the ability of GBS to translocate through an epithelial monolayer was also analysed. As shown in Figure 31, a GBS 80 knockout mutant strain partially loses the ability to translocate through an epithelial monolayer. Here epithelial monolayers were inoculated with wildtype or knockout mutant in the apical chamber of a transwell system for two hours and then non-adherent bacteria were washed off. Infection was prolonged for a further two and four hours. Samples were taken from the media of the basolateral side and the number of colony forming unties measured. Transepithelial electrical resistance measured prior to and after infection gave comparable values, indicating the maintenance of the integrity of the monolayer. By the six hour time point, the $\Delta 80$ mutants demonstrated a reduced percent transcytosis.

A similar experiment was conducted with GBS 104 knock out mutants. Here, as shown in Figure 22, the $\Delta 104$ mutants also demonstrated a reduced percent transcytosis, indicating that the mutant strains translocate through an epithelial monolayer less efficiently than their isogenic wild type counterparts.

Applicants also studied the effect of AI proteins on the capacity of a GBS strain to invade J774 macrophage-like cells. Here, J774 cells were infected with GBS COH1 wild type or COH1 Δ GBS104 or COH1 Δ GBS80 isogenic mutants. After one hour of infection, non-adherent bacteria were washed off and intracellular bacteria were recovered at two, four and six hours post antibiotic treatment. At each time point, cells were lysed with 0.25% Triton X-100 and lysates plated on TSA plates. As shown in Figure 32, the Δ 104 mutant demonstrated a significantly reduced percent invasion compared to both the wild type and Δ 80 mutant.

Example 6: Hyperoligomeric structures comprising AI surface proteins GBS 80 and GBS 104.

This example illustrates hyperoligomeric structures comprising AI surface proteins GBS 80 and GBS 104. A GBS isolate COH1 (serotype III) was adapted to increase expression of GBS 80.

Figure 34 presents a regular negative stain electron micrograph of this mutant; no pilus or hyperoligomeric structures are distinguishable on the surface of the bacteria. When the EM stain is based on anti-GBS 80 antibodies labelled with 10 or 20 nm gold particles, the presence of GBS 80 throughout the hyperoligomeric structure is clearly indicated (Figures 36, 37 and 38). EM staining against GBS 104 (anti-GBS 104 antibodies labelled with 10 nm gold particles) also reveals the presence of GBS 104 primarily on or near the surface of the bacteria or potentially associated with bacterial peptidoglycans (Figure 39). Analysis of this same strain (over-expressing GBS 80) with a combination of both anti-GBS 80 (using 20 nm gold particles) and anti-GBS 104 (using 10 nm gold

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(see Figures 40 and 41).

Example 7: GBS 80 is necessary for polymer formation and GBS 104 and sortase SAG0648 are necessary for efficient pili assembly

particles) reveals the presence of GBS 104 on the surface and within the hyperoligomeric structures

This example demonstrates that GBS 80 is necessary for formation of polymers and that GBS 104 and sortase SAG0648 are necessary for efficient pili assembly. GBS 80 and GBS 104 polymeric assembly was systematically analyzed in Coh1 strain single knock out mutants of each of the relevant coding genes in AI-1 (GBS 80, GBS 104, GBS 52, sag0647, and sag0648). Figure 41 provides Western blots of total protein extracts (strains noted above lanes) probed with either anti-GBS 80 (left panel) sera or anti-GBS 104 sera (right panel) for each of these Coh1 and Coh1 knock out strains. (Coh1, wild type Coh1; Δ80, Coh1 with GBS 80 knocked out; Δ104, Coh1 with GBS 104 knocked out; Δ52, Coh1 with GBS 52 knocked out; Δ647, Coh1 with SAG0647 knocked out; Δ648, Coh1 with SAG0648 knocked out, Δ647-8, Coh1 with SAG0647 and SAG0648 knocked out; Δ80/pGBS80, Coh1 with GBS 80 knocked out but complemented with a high copy number plasmid expressing GBS 80. Asterisks identify the monomer of GBS 80 and GBS 104.)

The smear of immunoreactive material observed in the wild type strain, along with its disappearance in $\Delta 80$ and $\Delta 104$ mutants, is consistent with the notion that such high molecular weight structures are composed of covalently linked (SDS-resistant) GBS 80 and GBS 104 subunits. The immunoblotting with both anti-GBS 80 (α -GBS 80) and anti-GBS 104 (α -GBS 104) revealed that deletion of sortase SAG0648 also interferes with the assembly of high molecular weight species, whereas the knock out mutant of the second sortase (SAG0647), even if somehow reduced, still maintains the ability to form polymeric structures.

Total extracts form GBS were prepared as follows. Bacteria were grown in 50 ml of Todd-Hewitt broth (Difco) to an OD_{600nm} of 0.5-0.6 and successively pelleted. After two washes in PBS the pellet was resuspended and incubated 3 hours at 37°C with mutanolisin. Cells were then lysed with at

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least three freezing-thawing cycles in dry ice and a 37°C bath. The lysate was then centrifuged to eliminate the cellular debris and the supernatant was quantified. Approximately 40 μg of each protein extract was separated on SDS-PAGE. The gel was then subjected to immunoblotting with mice antisera and detected with chemiluminescence.

Example 8: GBS 80 is polymerized by an AI-2 sortase

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This example illustrates that GBS 80 can be polymerized not only by AI-1 sortases, but also by AI-2 sortases. Figure 42 shows total cell extract immunoblots of GBS 515 strain, which lacks AI-1. The left panel, where an anti-GBS 67 sera was used, shows that GBS 67 from AI-2 is assembled into high-molecular weight-complexes, suggesting the formation of a second type of pilus. The same high molecular structure is observed when GBS 80 is highly expressed by reintroducing the gene within a plasmid (pGBS 80). By using anti-GBS 80 (right panel) sera on the same extracts, again it is observed that, with GBS 80 over expression (515/pGBS 80), a high-molecular weight structure is assembled. This implies that, in the absence of AI-1 sortases, AI-2 sortases (SAG1405 and SAG1406) can complement the lacking function, still being able to assemble GBS 80 in a pilus structure.

Example 9: Coh1 produces a high molecular weight molecule, the GBS 80 pilin

This example illustrates that Coh1 produces a high molecular weight molecule, greater than 1000 kDa, which is the GBS 80 pilin. Figure 43 provides silver-stained electrophoretic gels that show that Coh1 produces two macromolecules. One of these macromolecules disappears in the Coh1 GBS 80 knock out cells, but does not disappear in the Coh1 GBS 52 knock out mutant cells. The last two lanes on the right were loaded with 15 times the amount loaded in the other lanes. This was done in order to be able to count the bands. By doing this, a conservative size estimate of the top bands was calculated by starting at 240 kDa and considering each of 14 higher bands as the result of consecutive additions of a GBS 80 monomer.

Coh1, wild type Coh1; Δ80, Coh1 cells with GBS 80 knocked out; Δ52, Coh1 cells with GBS 52 knocked out; Δ80/pGBS 80, Coh1 cells with GBS 80 knocked out and complemented with a high copy number construct expressing GBS 80.

Example 10. GBS 52 is a minor component of the GBS pilus

This example illustrates that GBS 52 is present in the GBS pilus and is a minor component of the pilus. Figure 45 shows an immunoblot of total cell extracts from a GBS Coh1 strain and a GBS Coh1 strain knocked out for GBS 52 (Δ 52). The total cell extracts were immunoblotted anti-GBS 80 antisera (left) and anti-GBS 52 antisera (right). Immunoblotting was performed using a 3-8% Trisacetate polyacrylamide gel (Invitrogen) which provided excellent separation of large molecular weight proteins (see figure 41). When the gel was incubated with anti-GBS 80 sera, the bands from the Coh1 wild-type strain appeared shifted when compared to the Δ 52 mutant. This observation

indicated a different size of the pilus polymeric components in the two strains. When the same gel was stripped and incubated with anti-GBS 52 sera the high-molecular subunits in the Coh1 wild-type strain showed similar molecular size of those in the correspondent lane in the left panel. These findings confirmed that GBS 52 is indeed associated with GBS 80 macro-molecular structures but represents a minor component of the GBS pilus.

Example 11: Pilus structures are present in the supernatant of GBS bacterial cultures

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This example illustrates that the pilus structure assembled in Coh1 GBS is present in the supernatant of a bacterial cell culture. Figure 46 shows an immunoblot where the protein extract of the supernatant from cultures of different GBS mutant strains (117 = Coh1 GBS 80 knockout; 159= Coh1 GBS 104 knockout; 202= Coh1 GBS 52 knockout; 206= Coh1 GBS sag0647 knockout; 208= Coh1 GBS sag0648 knockout; 197= Coh1 GBS sag0647/sag0648 knockout; 179= Coh1 GBS 80 knockout complemented with a high copy plasmid expressing GBS 80). GBS 80 antisera detects the presence of pilus structures in the appropriate Coh1 strains.

The protein extract was prepared as follows. Bacteria were grown in THB to an OD_{600nm} of 0.5-0.6 and the supernatant was separated from the cells by centrifugation. The supernatant was then filtered (Ø 0.2 μm) and 1 ml was added with 60% TCA for protein precipitation.

GBS pili were also extracted from the fraction of surface-exposed proteins in Coh1 strain and its GBS 80 knock out mutant as described hereafter. Bacteria were grown to an OD_{600nm} of 0.6 in 50 ml of THB at 37°C. Cells were washed once with PBS and the pellet was then resuspended in 0.1 M KPO4 pH 6.2, 40% sucrose, 10 mM MgCl2, 400U/ml mutanolysin and incubated 3 hours at 37°C. Protoplasts were separated by centrifugation and the supernatant was recovered and its protein content measured.

In order to study the dynamics of pilus production during different growth phases, 1 ml supernatant of a culture at different OD_{600nm} was TCA precipitated and loaded onto a 3-8% SDS-PAGE as described before. Figure 47 shows the corresponding Western blot with GBS 80 anti-sera. The first group of lanes (left five sample lanes) refer to a Coh1 strain growth (OD_{600nm} are noted above the lanes) whereas the second group of lanes (right five samples) are from a GBS 80 knock out strain over expressing GBS 80. The experiment shows that pilus macromolecular structures can be found in the supernatant in all of the growth phases tested.

Example 12: In GBS strain Coh1, only GBS 80 and a sortase (sag0647 or sag0648) is required for polymerization

This example describes requirements for pilus formation in Coh1. Figure 48 shows a Western blot of total protein extracts (prepared as described before) using anti-GBS 80 sera on Coh1 clones. (Coh1, wild type Coh1; Δ 104, Coh1 knocked out for GBS 104, Δ 647, Coh1 knocked out for sag0647, Δ 648, Coh1 knocked for sag0648, Δ 647-8, Coh1 knocked out for sag0647 and sag0648; 515, wild

type hacterial strain 515 which lacks an Al-1; p80 a high copy number plasmid which expresses GBS 80.) The data show that only the double sortase mutant is unable to polymerize GBS 80 indicating that the 'conditio sine qua non' for pilus polymerization is the co-existence of GBS 80 with at least one sortase. This result leads to a reasonable assumption that SAG1405 and SAG1406 are responsible for polymerization in this strain.

Example 13: GBS 80 can be expressed in *L. lactis* under its own promoter and terminator sequences

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This example demonstrates that *L. lactis*, a non-pathogenic bacterium, can express GBS AI

polypeptides such as GBS 80. *L. lactis* M1363 (*J. Bacteriol. 154* (1983):1-9) was transformed with a construct encoding GBS 80. Briefly, the construct was prepared by cloning a DNA fragment containing the gene coding for GBS 80 under its own promoter and terminator sequences into plasmid pAM401 (a shuttle vector for *E. coli* and other Gram positive bacteria; *J. Bacteriol. 163* (1986):831-836). Total extracts of the transformed bacteria in log phase were separated on SDS-PAGE, transferred to membranes, and incubated with antiscrum against GBS 80. A polypeptide corresponding to the molecular weight of GBS 80 was detected in the lanes containing total extracts of *L. lactis* transformed with the GBS 80 construct. See Figures 133A and 133B, lanes 6 and 7. This same polypeptide was not detected in the lane containing total extracts of *L. lactis* not transformed with the GBS 80 construct, lane 9. This example shows that *L. lactis* can express GBS 80 under its own promoter and terminator.

Example 14: L. lactis modified to express GBS AI-1 under the GBS 80 promoter and terminator sequences expresses GBS 80 in polymeric structures

This example demonstrates the ability of *L. lactis* to express GBS AI-1 polypeptides and to incorporate at least some of the polypeptides into oligomers. *L. lactis* was transformed with a construct containing the genes encoding GBS AI-1 polypeptides. Briefly, the construct was prepared by cloning a DNA fragment containing the genes for GBS 80, GBS 52, SAG0647, SAG0648, and GBS 104 under the GBS 80 promoter and terminator sequences into construct pAM401. The construct was transformed into *L. lactis* M1363. Total extracts of log phase transformed bacteria were separated on reducing SDS-PAGE, transferred to membranes, and incubated with antiserum against GBS 80. A polypeptide with a molecular weight corresponding to the molecular weight of GBS 80 was detected in the lanes containing *L. lactis* transformed with the GBS AI-1 encoding construct. See Figure 134, lane 2. In addition, the same lane also showed immunoreactivity of polypeptides having higher molecular weights than the polypeptide having the molecular weight of GBS 80. These higher molecular weight polypeptides are likely oligomers of GBS 80. Oligomers of similar molecular

weights were also observed on a Western hot of the culture supernatant of the transformed L. lactis. See lane 4 of Figure 135. Thus, this example shows that L. lactis transformed to express GBS AI-1 can efficiently polymerize GBS 80 in the form of a pilus. This pilus structure can likely be purified from either the cell culture supernatant or cell extracts.

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Example 15: Cloning and Expression of S. pneumoniae Sp0462

This example describes the production of a clone encoding a Sp0462 polypeptide and expression of the clone. To produce a clone encoding Sp0462, the open reading frame encoding Sp0462 was amplified using primers that annealed within the full-length Sp0462 open reading frame sequence. Figure 150A provides a 893 amino acid sequence of Sp0462. The primers used to produce a clone encoding the Sp0462 polypeptide are shown in Figure 150B. These primers annealed to the nucleotide sequences encoding the amino acid residues indicated by underlining in Figure 150A. Amplification of the open reading frame encoding Sp0462 using these primers produced the amplicon shown at lane 2 of the agarose gel provided in Figure 160. The Sp0462 clone encodes amino acid residues 38-862 of the 893 amino acid residue Sp0462 protein; the italicized residues in Figure 150A were eliminated. Figure 151A provides a schematic depiction of the recombinant Sp0462 polypeptide. Figure 151B shows a schematic depiction of the full-length Sp0462 polypeptide. Both the recombinant Sp0462 encoded by the clone and the full-length Sp0462 protein have two collagen binding protein type B (Cna B) domains and a von Hillebrand factor A (vWA) domain. The cloned recombinant Sp0462 lacks the LPXTG motif present in the full-length Sp0462 protein. Western blot analysis for expression of the Sp0462 clone did not result in detection of polypeptides with serum obtained from S. pneumoniae-infected patients (Figure 152A) or GBS 80 antiserum (Figure 152B).

Example 16: Cloning and Expression of S. pneumoniae Sp0463

This example describes the production of a clone encoding a Sp0463 polypeptide and detection of recombinant Sp0463 polypeptide expressed from the clone. To produce a clone encoding Sp0463, the open reading frame encoding Sp0463 was amplified using primers that annealed within the full-length Sp0463 open reading frame sequence. Figure 153A provides a 665 amino acid sequence of Sp0463. The primers used to produce the clone encoding Sp0463 polypeptide are shown in Figure 153B. These primers annealed to the nucleotide sequences encoding the amino acid residues indicated by underlining in Figure 153A. Amplification of the open reading frame encoding Sp0463 using these primers produced the amplicon shown at lane 3 of the agarose gel provided in Figure 160. The Sp0463 clone encodes amino acid residues 23-627 of the 665 amino acid residue Sp0463 protein; the italicized residues in Figure 153A were eliminated. Figure 154A provides a schematic depiction of the recombinant Sp0463 polypeptide. Figure 154B shows a schematic depiction of the full-length Sp0463 polypeptide. Both the recombinant Sp0463 encoded by the clone and the full-length Sp0463 protein have a Cna B domain and an E box motif. The cloned recombinant

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Sp0463 lacks the PXTC motif present in the full-length Sp0463 protein. Expression of the Sp0463 clone resulted in the detection of a 60 kD polypeptide, the expected molecular weight of the recombinant Sp0463 polypeptide, by Western blot analysis. See Figure 155.

Example 17: Cloning and Expression of S. pneumoniae Sp0464

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This example describes the production of a clone encoding a Sp0464 polypeptide and detection of recombinant Sp0464 polypeptide expressed from the clone. To produce a clone encoding Sp0464, the open reading frame encoding Sp0464 was amplified using primers that annealed either within the full-length Sp0464 open reading frame sequence. Figure 157A provides a 393 amino acid sequence of Sp0464. The primers used to produce a clone encoding the Sp0464 polypeptide are shown in Figure 157B. These primers annealed to the nucleotide sequences encoding the amino acid residues indicated by underlining in Figure 157A. Amplification of the open reading frame encoding Sp0464 using these primers produced the amplicon shown at lane 4 of the agarose gel provided in Figure 160. The Sp0464 clone encodes amino acid residues 19-356 of the 393 amino acid residue Sp0464 protein; the italicized residues in Figure 157A were eliminated. Figure 158A provides a schematic depiction of the recombinant Sp0464 polypeptide. Figure 158B shows a schematic depiction of the full-length Sp0464 polypeptide. Both the recombinant Sp0464 encoded by the clone and the full-length Sp0464 protein have two Cna B domains. The cloned recombinant Sp0464 lacks the LPXTG motif present in the full-length Sp0464 protein. Expression of the Sp0464 clone resulted in the detection of a 38 kD polypeptide, the expected molecular weight of the recombinant Sp0464 polypeptide, by Western blot analysis. See Figure 159.

Example 18: Intranasal Immunization of Mice with Recombinant L. lactis Expressing GBS 80 and Subsequent Challenge

This example describes a method of intranasally immunizing mice using L. lactis that express GBS 80. Intranasal immunization consisted of 3 doses at days 0, 14 and 28, each dose administered in three consecutive days. Each day, groups of 3 CD-1 outbred female mice 6-7 weeks old (Charles River Laboratories, Calco Italy) were immunized intranasally with 10^9 or 10^{10} CFU of the recombinant Lactococcus lactis suspended in 20 μ l of PBS. In each immunization scheme negative (wild-type L. lactis) and positive (recombinant GBS80) control groups were used. The immune response of the dams was monitored by using serum samples taken on day 0 and 49. The female mice were bred 2-7 days after the last immunization (at approximately t=36-37), and typically had a gestation period of 21 days. Within 48 hours of birth, the pups were challenged via I.P. with GBS in a dose approximately equal to an amount which would be sufficient to kill 90 % of immunized pups (as determined by empirical data gathered from PBS control groups). The GBS challenge dose is preferably administered in 50ml of THB medium. Preferably, the pup challenge takes place at 56 to 61 days after the first immunization. The challenge inocula were prepared starting from frozen

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WO 2006/078318 PCT/US2 cultures diluted to the appropriate concentration with THB prior to use. Survival of pups was monitored for 5 days after challenge.

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Example 19: Subcutaneous Immunization of Mice with Recombinant L. lactis Expressing GBS 80 and Subsequent Challenge

This example describes a method of subcutaneous immunization mice using L. lactis that express GBS 80. Subcutaneous immunization consists of 3 doses at days 0, 14 and 28. Groups of 3 CD-1 outbred female mice 6-7 weeks old (Charles River Laboratories, Calco Italy) were injected subcutaneously with 109 or 1010 CFU of the recombinant Lactococcus lactis suspended in 100 μl of PBS. In each immunization scheme, negative (wild-type L. lactis) and positive (recombinant GBS80) control groups were used. The immune response of the dams was monitored by using serum samples taken on day 0 and 49. The female mice were bred 2-7 days after the last immunization (at approximately t=36-37), and typically had a gestation period of 21 days. Within 48 hours of birth, the pups were challenged via I.P. with GBS in a dose approximately equal to an amount which would be sufficient to kill 90 % of immunized pups (as determined by empirical data gathered from PBS control groups). The GBS challenge dose is preferably administered in 50ml of THB medium. Preferably, the pup challenge takes place at 56 to 61 days after the first immunization. The challenge inocula were prepared starting from frozen cultures diluted to the appropriate concentration with THB prior to use. Survival of pups was monitored for 5 days after challenge.

Example 20: Immunization of Mice with GAS AI polypeptides and Subsequent Intranasal Challenge

This example describes a method of immunizing mice with GAS AI polypeptides and subsequently intranasally challenging the mice with GAS bacteria. Groups of 10 CD1 female mice aged between 6 and 7 weeks are immunized with a combination of GAS antigens of the invention GAS 15, GAS 16, and GAS 18, (15 µg of each recombinant antigen, derived from M1 strain SF370) or L. lactis expressing the M1 strain SF370 adhesin island, suspended in 100 µl of suitable solution. Each group receives 3 doses at days 0, 21 and 45. Immunization is performed through subcutaneous or intraperitoneal injection for the GAS 15, GAS 16, GAS 18 protein combination. The protein combination is administered with an equal volume of Complete Freund's Adjuvant (CFA) for the first dose and Incomplete Freund's Adjuvant (IFA) for the following two doses. Immunization is performed intranasally for the L. lactis expressing the M1 strain SF370 adhesin island. In each immunization scheme negative and positive control groups are used.

The negative control group for the mice immunized with the GAS 15, GAS 16, GAS 18 protein combination included mice immunized with PBS. The negative control group for the mice immunized with L. lactis expressing the M1 strain SF370 adhesin island, included mice immunized

with either wildlypell vacus or L. vacus transformed with the pAM401 expression vector lacking any cloned adhesin island sequence.

The positive control groups included mice immunized with purified M1 strain SF370 M protein.

Immunized mice are then anaesthetized with Zoletil and challenged intranasally with a 25 μ L suspension containing 1.2 x 10⁶ or 1.2 x 10⁸ CFU of ISS 3348 in THB. Animals are observed daily and checked for survival.

Example 21: Active Maternal Immunization Assay

As used herein, an Active Maternal Immunization assay refers to an *in vivo* protection assay where female mice are immunized with the test antigen composition. The female mice are then bred and their pups are challenged with a lethal dose of GBS. Serum titers of the female mice during the immunization schedule are measured as well as the survival time of the pups after challenge.

Mouse immunization

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Specifically, groups of 4 CD-1 outbred female mice 6-8 weeks old (Charles River Laboratories, Calco Italy) are immunized with one or more GBS antigens, (20 µg of each recombinant GBS antigen), suspended in 100 µl of PBS. Each group receives 3 doses at days 0, 21 and 35. Immunization is performed through intra-peritoneal injection of the protein with an equal volume of Complete Freund's Adjuvant (CFA) for the first dose and Incomplete Freund's Adjuvant (IFA) for the following two doses. In each immunization scheme negative and positive control groups are used.

Immune response is monitored by using serum samples taken on day 0 and 49. The sera are analyzed as pools from each group of mice.

25 Active maternal immunization

A maternal immunization/neonatal pup challenge model of GBS infection was used to verify the protective efficacy of the antigens in mice. The mouse protection study was adapted from Rodewald et al. (Rodewald et al. J. Infect. Diseases 166, 635 (1992)). In brief, CD-1 female mice (6-8 weeks old) were immunized before breeding, as described above. The mice received 20 µg of protein per dose when immunized with a single antigen and 60 µg of protein per dose (15 µg of each antigen) when immunized with the combination of antigens. Mice were bred 2-7 days after the last immunization. Within 48 h of birth, pups were injected intraperitoneally with 50 µl of GBS culture. Challenge inocula were prepared starting from frozen cultures diluted to the appropriate concentration with THB before use. In preliminary experiments (not shown), the challenge doses per pup for each strain tested were determined to cause 90% lethality. Survival of pups was monitored for 2 days after challenge. Protection was calculated as (percentage

dead Control minus percentage dead vaccine) divided by percentage dead Control multiplied by 100. Data were evaluated for statistical significance by Fisher's exact test.

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The invention encompasses, but is not limited to, the embodiments enumerated below.

- 1. An immunogenic composition comprising a purified Group B Streptococcus (GBS) adhesin island (AI) polypeptide in oligomeric form.
- 2. The immunogenic composition of embodiment 1 wherein the GBS AI polypeptide is selected from a GBS AI-1.
- 3. The immunogenic composition of embodiment 1 wherein the GBS AI polypeptide is selected from a GBS AI-2.
- 1. An immunogenic composition comprising a purified Group B Streptococcus (GBS) adhesin island (AI) polypeptide in oligomeric form.
- 2. The immunogenic composition of embodiment 1 wherein the GBS AI polypeptide is selected from a GBS AI-1.
- 3. The immunogenic composition of embodiment 1 wherein the GBS AI polypeptide is selected from a GBS AI-2.
- 4. The immunogenic composition of any of embodiments 1-3 wherein the GBS AI polypeptide comprises a sortase substrate motif.
- 5. The immunogenic composition of embodiment 4 wherein the sortase substrate motif is an LPXTG motif.
- 6. The immunogenic composition of embodiment 5 wherein the LPXTG motif is represented by the amino acid sequence XPXTG, wherein the X at amino acid position 1 is an L, an I, or an F and the X at amino acid position 3 is any amino acid residue.
- 7. The immunogenic composition of any one of embodiments 1-3 wherein the GBS AI polypeptide affects the ability of GBS bacteria to adhere to epithelial cells.
- 8. The immunogenic composition of any one of embodiments 1-3 wherein the GBS AI polypeptide affects the ability of GBS bacteria to invade epithelial cells.
- 9. The immunogenic composition of any one of embodiments 1-3 wherein the GBS AI polypeptide affects the ability of GBS bacteria to translocate through an epithelial cell layer.
- 10. The immunogenic composition of any one of embodiments 1-3 wherein the GBS AI polypeptide is capable of associating with an epithelial cell surface.
- 11. The immunogenic composition of embodiment 10 wherein the associating with an epithelial cell surface is binding to the epithelial cell surface.
 - 12. The immunogenic composition of any of embodiments 1-3 wherein the GBS AI polypeptide is a full-length GBS AI protein.
- 13. The immunogenic composition of any of embodiments 1-3 wherein the GBS AI polypeptide is a fragment of a full-length GBS AI protein.
- 14. The immunogenic composition of embodiment 13 wherein the fragment comprises at least 7 contiguous amino acid residues of the GBS AI protein.

The impunogenic composition of embodiment 2 wherein the GBS AI polypeptide is selected from the group consisting of GBS 80, GBS 104, GBS 52, and fragments thereof.

16. The immunogenic composition of embodiment 3 wherein the GBS AI polypeptide is selected from the group consisting of GBS 59, GBS 67, GBS 150, 01521, 01523, 01524, and fragments thereof.

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- 17. The immunogenic composition of embodiment 15 wherein the GBS AI polypeptide is GBS 80.
- 18. The immunogenic composition of any of embodiments 1-3 or 15-17 wherein the oligomeric form is a hyperoligomer.
- 19. The immunogenic composition of any of embodiments 1-3, or 15-17 further comprising a Gram positive bacterium antigen not associated with an AI.
- 20. The immunogenic composition of embodiment 19 wherein the antigen is selected from the group consisting of GBS 322 and GBS 276.
 - 21. The immunogenic composition of embodiment 20 wherein the antigen is GBS 322.
- 22. An immunogenic composition comprising a purified Gram positive bacteria adhesin island (AI) polypeptide in an oligomeric form.
 - 23. The immunogenic composition of embodiment 22 wherein the Gram positive bacteria is of a genus selected from the group consisting of *Streptococcus*, *Enterococcus*, *Staphylococcus*, or *Listeria*.
- 24. The immunogenic composition of embodiment 23 wherein the Gram positive bacteria is of the genus *Streptococcus*.
 - 25. The immunogenic composition of any of embodiments 22-24 wherein the Gram positive bacteria AI polypeptide comprises a sortase substrate motif.
- 26. The immunogenic composition of embodiment 25 wherein the sortase substrate motif is an LPXTG motif.
 - 27. The immunogenic composition of any one of embodiments 22-24 wherein the Gram positive bacteria AI polypeptide affects the ability of Gram positive bacteria to adhere to epithelial cells.
 - 28. The immunogenic composition of any one of embodiments 22-24 wherein the Gram positive bacteria AI polypeptide affects the ability of Gram positive bacteria to invade epithelial cells.
 - 29. The immunogenic composition of any one of embodiments 22-24 wherein the Gram positive bacteria AI polypeptide affects the ability of Gram positive bacteria to translocate through an epithelial cell layer.
- 30. The immunogenic composition of any one of embodiments 22-24 wherein the Gram positive bacteria AI polypeptide is capable of associating with an epithelial cell surface.
 - 31. The immunogenic composition of embodiment 30 wherein the associating with an epithelial cell surface is binding to the epithelial cell surface.

32. The immunogenic composition of any of embodiments 22-24 wherein the Gram positive bacteria AI polypeptide is a full-length Gram positive bacteria AI protein.

- 33. The immunogenic composition of any of embodiments 22-24 wherein the Gram positive bacteria AI polypeptide is a fragment of a full-length Gram positive bacteria AI protein.
- 34. The immunogenic composition of embodiment 33 wherein the fragment comprises at least 7 contiguous amino acid residues of the Gram positive bacteria AI protein.

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- 35. The immunogenic composition of embodiment 24 wherein the genus *Streptococcus* bacteria is Group A Streptococcus (GAS) bacteria and the Gram positive bacteria AI polypeptide is a GAS AI polypeptide.
- 36. The immunogenic composition of embodiment 35 wherein the GAS AI polypeptide is selected from a GAS AI-1.
 - 37. The immunogenic composition of embodiment 35 wherein the GAS AI polypeptide is selected from a GAS AI-2.
- 38. The immunogenic composition of embodiment 35 wherein the GAS AI polypeptide is selected from a GAS AI-3.
 - 39. The immunogenic composition of embodiment 35 wherein the GAS AI polypeptide is selected from a GAS AI-4.
 - 40. The immunogenic composition of any of embodiments 35-39 wherein the GAS AI polypeptide comprises a sortase substrate motif.
- 41. The immunogenic composition of embodiment 40 wherein the sortase substrate motif is an LPXTG motif.
 - 42. The immunogenic composition of embodiment 41 wherein the LPXTG motif is represented by XXXXG, wherein the X at the first amino acid position is an L, a V, an E, or a Q, wherein the X at the second amino acid position is P if the X at the first amino acid position is an L, the X at the second amino acid position is a V if the X at the first amino acid position is an E or a Q, or the X at the second amino acid position is a V or a P if the X at the first amino acid position is a V, wherein the X at the third amino acid position is any amino acid residue, and wherein the X at the fourth amino acid position is a T if the X at the first amino acid position is a V, an E, or a Q, or the X at the fourth amino acid position is a T, an S, or an A if the X at the first amino acid position is an L.
 - 43. The immunogenic composition of any one of embodiments 35-39 wherein the GAS AI polypeptide affects the ability of GAS bacteria to adhere to epithelial cells.
 - 44. The immunogenic composition of any one of embodiments 35-39 wherein the GAS AI polypeptide affects the ability of GAS bacteria to invade epithelial cells.
 - 45. The immunogenic composition of any one of embodiments 35-39 wherein the GAS AI polypeptide affects the ability of GAS bacteria to translocate through an epithelial cell layer.
 - 46. The immunogenic composition of any one of embodiments 35-39 wherein the GAS AI polypeptide is capable of associating with an epithelial cell surface.

The immunogenic composition of embodiment 46 wherein the associating with an epithelial cell surface is binding to the epithelial cell surface.

- 48. The immunogenic composition of any of embodiments 35-39 wherein the GAS AI polypeptide is a full-length GAS AI protein.
- 49. The immunogenic composition of any of embodiments 35-39 wherein the GAS AI polypeptide is a fragment of a full-length GAS AI protein.

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- 50. The immunogenic composition of embodiment 49 wherein the fragment comprises at least 7 contiguous amino acid residues of the GAS AI protein.
- 51. The immunogenic composition of embodiment 36 wherein the GAS AI-1 polypeptide is selected from the group consisting of M6_Spy0157, M6_Spy0159, M6_Spy0160, CDC SS 410_fimbrial, ISS3650 fimbrial, DSM2071 fimbrial, and fragments thereof.
- 52. The immunogenic composition of embodiment 37 wherein the GAS AI-2 polypeptide is selected from the group consisting of GAS15, GAS16, GAS18, and fragments thereof.
- 53. The immunogenic composition of embodiment 38 wherein the GAS AI-3 polypeptide is selected from the group consisting of SpyM3_0098, SpyM3_0100, SpyM3_0102, SpyM3_0104, SPs0100, SPs0102, SPs0104, SPs0106, orf78, orf80, orf82, orf84, spyM18_0126, spyM18_0128, spyM18_0130, spyM18_0132, SpyoM01000156, SpyoM01000155, SpyoM01000154, SpyoM01000153, SpyoM01000152, SpyoM01000151, SpyoM01000150, SpyoM01000149, ISS3040_fimbrial, ISS3776_fimbrial, ISS4959_fimbrial, and fragments thereof.
- 53. The immunogenic composition of embodiment 39 wherein the GAS AI-4 polypeptide is selected from the group consisting of 19224134, 19224135, 19224137, 19224139, 19224141, 20010296_fimbrial, 20020069_fimbrial, CDC SS 635_fimbrial, ISS4883_fimbrial, ISS4538_fimbrial, and fragments thereof.
- 54. The immunogenic composition of embodiment 24 wherein the *Streptococcus* bacteria is *Streptococcus pneumoniae* and the Gram positive bacteria AI polypeptide is a *S. pneumoniae* AI polypeptide.
- 55. The immunogenic composition of embodiment 54 wherein the *S. pneumoniae* AI polypeptide comprises a sortase substrate motif.
- 56. The immunogenic composition of embodiment 55 wherein the sortase substrate motif is an LPXTG motif.
 - 57. The immunogenic composition of embodiment 54 wherein the S. pneumoniae AI polypeptide affects the ability of S. pneumoniae to adhere to epithelial cells.
 - 58. The immunogenic composition of embodiment 54 wherein the S. pneumoniae AI polypeptide affects the ability of S. pneumoniae to invade epithelial cells.
 - 59. The immunogenic composition of embodiment 54 wherein the *S. pneumoniae* AI polypeptide affects the ability of *S. pneumoniae* to translocate through an epithelial cell layer.
 - 60. The immunogenic composition of embodiment 54 wherein the S. pneumoniae AI polypeptide is capable of associating with an epithelial cell surface.

The immunogenic composition of embodiment 60 wherein the associating with an epithelial cell surface is binding to the epithelial cell surface.

- 62. The immunogenic composition of embodiment 54 wherein the *S. pneumoniae* AI polypeptide is a full-length *S. pneumoniae* AI protein.
- 63. The immunogenic composition of embodiment 54 wherein the *S. pneumoniae* AI polypeptide is a fragment of a full-length *S. pneumoniae* AI protein.

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- 64. The immunogenic composition of embodiment 63 wherein the fragment comprises at least 7 contiguous amino acid residues of the *S. pneumoniae* AI protein.
- 65. The immunogenic composition of embodiment 54 wherein the *S. pneumoniae* AI polypeptide is selected from the group consisting of SP0462, SP0463, SP0464, orf3_670, orf4_670, orf5_670, ORF3_14CSR, ORF4_14CSR, ORF5_14CSR, ORF3_19AH, ORF4_19AH, ORF5_19AH, ORF3_19FTW, ORF4_19FTW, ORF5_19FTW, ORF3_23FP, ORF4_23FP, ORF5_23FP, ORF3_23FTW, ORF4_23FTW, ORF5_23FTW, ORF3_6BF, ORF4_6BF, ORF5_6BF, ORF3_6BSP, ORF4_6BSP, ORF5_6BSP, ORF5_6BSP, ORF4_6BSP, ORF5_6BSP, ORF5_
 - 66. The immunogenic composition of any one of embodiments 22-24, 35-39, 51-54, or 65 wherein the oligomeric form is a hyperoligomer.
 - 67. The immunogenic composition of any one of embodiments 22-24, 35-39, 51-54, or 65 further comprising a Gram positive bacteria antigen not associated with an AI.
- 68. The immunogenic composition of embodiment 67 wherein the antigen is selected from the group consisting of GBS 322 and GBS 276.
 - 69. An immunogenic composition comprising a first and a second Group B Streptococcus (GBS) adhesin island (AI) polypeptide.
 - 70. The immunogenic composition of embodiment 69 wherein a full-length polynucleotide sequence encoding for the first GBS AI polypeptide is not present in a GBS bacteria genome comprising a polynucleotide sequence encoding for the second GBS AI polypeptide.
 - 71. The immunogenic composition of embodiment 69 wherein polynucleotides encoding the first and the second GBS AI polypeptide are each present in genomes of more than one GBS serotype and strain isolate.
- 72. The immunogenic composition of embodiment 69 wherein the first GBS AI polypeptide 30 is encoded by a GBS AI-1.
 - 73. The immunogenic composition of embodiment 69 wherein the first GBS AI polypeptide is encoded by a GBS AI-2.
 - 74. The immunogenic composition of embodiment 72 wherein the second GBS AI polypeptide is encoded by a GBS AI-2.
- 75. The immunogenic composition of embodiment 73 wherein the second GBS AI polypeptide is encoded by a GBS AI-2.
 - 76. The immunogenic composition of embodiment 72 wherein the second GBS AI polypeptide is encoded by a GBS AI-1.

polypeptide is encoded by a GBS AI-1.

- 78. The immunogenic composition of embodiment 72 wherein the first GBS AI polypeptide is selected from the group consisting of GBS 80, GBS 104, GBS 52, and fragments thereof.
- 79. The immunogenic composition of embodiment 73 wherein the first GBS AI polypeptide is selected from the group consisting of GBS 59, GBS 67, GBS 150, 01521, 01523, 01524, and fragments thereof.

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- 80. The immunogenic composition of embodiment 74 or 75 wherein the second GBS AI polypeptide is selected from the group consisting of GBS 59, GBS 67, GBS 150, 01521, 01523, 01524, and fragments thereof, and wherein the first and the second GBS AI polypeptide are not the same polypeptide.
- 81. The immunogenic composition of embodiment 76 or 77 wherein the second GBS AI polypeptide is selected from the group consisting of GBS 80, GBS 104, GBS 52, and fragments thereof, and wherein the first and the second GBS AI polypeptide are not the same polypeptide.
- 82. The immunogenic composition of any one of embodiments 69-77 wherein the first GBS AI polypeptide comprises a sortase substrate motif.
- 83. The immunogenic composition of embodiment 82 wherein the sortase substrate motif is an LPXTG motif.
- 84. The immunogenic composition of embodiment 83 wherein the LPXTG motif is represented by the sequence XPXTG, wherein the X at amino acid position 1 is an L, an I, or an F and the X at amino acid position 3 is any amino acid residue.
- 85. The immunogenic composition of any one of embodiments 69-77 wherein the first GBS AI polypeptide affects the ability of GBS bacteria to adhere to epithelial cells.
- 86. The immunogenic composition of any one of embodiments 69-77 wherein the first GBS AI polypeptide affects the ability of GBS bacteria to invade epithelial cells.
- 87. The immunogenic composition of any one of embodiments 69-77 wherein the first GBS AI polypeptide affects the ability of GBS bacteria to translocate through an epithelial cell layer.
- 88. The immunogenic composition of any one of embodiments 69-77 wherein the first GBS AI polypeptide is capable of associating with an epithelial cell surface.
- 89. The immunogenic composition of embodiment 88 wherein the associating with an epithelial cell surface is binding to the epithelial cell surface.
- 90. The immunogenic composition of any of embodiments 69-77 wherein the first GBS AI polypeptide is a full-length GBS AI protein.
- 91. The immunogenic composition of any of embodiments 69-77 wherein the first GBS AI polypeptide is a fragment of a full-length GBS AI protein.
 - 92. The immunogenic composition of embodiment 91 wherein the fragment comprises at least 7 contiguous amino acid residues of the first GBS AI protein.

AI polypeptide is in oligomeric form.

- 94. The immunogenic composition of any one of embodiments 69-77 wherein the second GBS AI polypeptide is in oligomeric form.
- 95. The immunogenic composition of any one of embodiments 69-79 wherein the first and the second GBS AI polypeptide are associated in a single oligomeric form.

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- 96. The immunogenic composition of embodiment 95 wherein the first and the second GBS AI polypeptides are chemically associated.
- 97. The immunogenic composition of embodiment 95 wherein the first and the second GBS AI polypeptides are physically associated.
 - 98. The immunogenic composition of embodiment 93 wherein the oligomeric form is a hyperoligomer.
 - 99. The immunogenic composition of embodiment 94 wherein the oligomeric form is a hyperoligomer.
- 15 100. The immunogenic composition of embodiment 76 wherein the first GBS AI polypeptide is GBS 80 and the second GBS AI polypeptide is GBS 104.
 - 101. The immunogenic composition of embodiment 74 wherein the first GBS AI polypeptide is GBS 80 and the second GBS AI polypeptide is GBS 67.
- 102. The immunogenic composition of any one of embodiments 69-79, 100, or 101 further comprising a GBS polypeptide not associated with an AI.
 - 103. The immunogenic composition of embodiment 102 wherein the GBS polypeptide not associated with an AI is selected from the group consisting of GBS 322 and GBS 276.
 - 104. The immunogenic composition of embodiment 103 wherein the GBS polypeptide not associated with an AI is GBS 322.
- 25 105. An immunogenic composition comprising a first and a second Gram positive bacteria adhesin island (AI) polypeptide.
 - 106. The immunogenic composition of embodiment 105 wherein a full length polynucleotide sequence encoding for the first Gram positive bacteria AI polypeptide is not present in a genome of a Gram positive bacteria comprising a full length polynucleotide sequence encoding for the second Gram positive bacteria AI polypeptide.
 - 107. The immunogenic composition of embodiment 105 wherein polynucleotides encoding the first and the second Gram positive bacteria AI polypeptide are each present in genomes of more than one Gram positive bacteria serotype and strain isolate.
 - 108. The immunogenic composition of embodiment 105 wherein the first and the second Gram positive bacteria AI polypeptides are of different Gram positive bacteria species.
 - 109. The immunogenic composition of embodiment 105 wherein the first and the second Gram positive bacteria AI polypeptides are of the same Gram positive bacteria species.

Gram positive bacteria AI polypeptides are from different AI subtypes.

111. The immunogenic composition of embodiment 105 wherein the first and the second Gram positive bacteria AI polypeptides are from the same AI subtype.

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- 112. The immunogenic composition of embodiment 105 wherein the first Gram positive bacteria AI polypeptide has detectable surface exposure on a first Gram positive bacteria strain or serotype but not a second Gram positive bacteria strain or subtype and the second Gram positive bacteria AI polypeptide has detectable surface exposure on the second Gram positive bacteria strain or serotype but not the first Gram positive bacteria strain or serotype.
- 113. The immunogenic composition of embodiment 105 wherein the Gram positive bacteria is S. pneumonaie, S. mutans, E. faecalis, E. faecium, C. difficile, L. monocytogenes, or C. diphtheriae.
- 114. The immunogenic composition of any of embodiments 105-113 wherein the first and the second Gram positive bacteria AI polypeptides comprise a sortase substrate motif.
- 115. The immunogenic composition of embodiment 114 wherein the sortase substrate motif is an LPXTG motif.
- 116. The immunogenic composition of embodiment 115 wherein the LPXTG motif is represented by XXXXG, wherein the X at amino acid position 1 is an L, a V, an E, an I, an F, or a Q, wherein X at amino acid position 2 is a P if X at amino acid position 1 is an L, an I, or an F, wherein X at amino acid position 2 is a V if X at amino acid position 1 is a E or a Q, wherein X at amino acid position 2 is a V or a P if X at amino acid position 1 is a V, wherein X at amino acid position 3 is any amino acid residue, wherein X at amino acid position 4 is a T if X at amino acid position 1 is a V, E, I, F, or Q, and wherein X at amino acid position 4 is a T, S, or A if X at amino acid position 1 is an L.
- 117. The immunogenic composition of embodiment 105 wherein the first Gram positive bacteria AI polypeptide is a first Group A Streptococcus (GAS) AI polypeptide.
- 118. The immunogenic composition of embodiment 117 wherein the first GAS AI polypeptide comprises a sortase substrate motif.
- 119. The immunogenic composition of embodiment 118 wherein the sortase substrate motif is an LPXTG motif.
- 120. The immunogenic composition of embodiment 119 wherein the LPXTG motif is represented by XXXXG, wherein the X at the first amino acid position is an L, a V, an E, or a Q, wherein the X at the second amino acid position is P if the X at the first amino acid position is an L, the X at the second amino acid position is a V if the X at the first amino acid position is an E or a Q, or the X at the second amino acid position is a V or a P if the X at the first amino acid position is a V, wherein the X at the third amino acid position is any amino acid residue, and wherein the X at the fourth amino acid position is a T if the X at the first amino acid position is a V, an E, or a Q, or the X at the fourth amino acid position is a T, an S, or an A if the X at the first amino acid position is an L.
- 121. The immunogenic composition of embodiment 117 wherein the first GAS AI polypeptide affects the ability of GAS bacteria to adhere to epithelial cells.

polypeptide affects the ability of GAS bacteria to invade epithelial cells.

- 123. The immunogenic composition of embodiment 117 wherein the first GAS AI polypeptide affects the ability of GAS bacteria to translocate through an epithelial cell layer.
- 124. The immunogenic composition of embodiment 117 wherein the first GAS AI polypeptide is capable of associating with an epithelial cell surface.

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- 125. The immunogenic composition of embodiment 117 wherein the associating with an epithelial cell surface is binding to the epithelial cell surface.
- 126. The immunogenic composition of embodiment 117 wherein the first GAS AI polypeptide is a full-length GAS AI protein.
 - 127. The immunogenic composition of embodiment 117 wherein the first GAS AI polypeptide is a fragment of a full-length GAS AI protein.
 - 128. The immunogenic composition of embodiment 127 wherein the fragment comprises at least 7 contiguous amino acid residues of the GAS AI protein.
- 15 129. The immunogenic composition of embodiment 117 wherein the first GAS AI polypeptide is a first GAS AI-1 polypeptide.
 - 130. The immunogenic composition of embodiment 117 wherein the first GAS AI polypeptide is a first GAS AI-2 polypeptide.
- 131. The immunogenic composition of embodiment 117 wherein the first GAS AI20 polypeptide is a first GAS AI-3 polypeptide.
 - 132. The immunogenic composition of embodiment 117 wherein the first GAS AI polypeptide is a first GAS AI-4 polypeptide.
 - 133. The immunogenic composition of any one of embodiments 117 or 129-132 wherein the second Gram positive bacteria AI polypeptide is a second GAS AI polypeptide.
 - 134. The immunogenic composition of embodiment 133 wherein the second GAS AI polypeptide is a second GAS AI-1 polypeptide.
 - 135. The immunogenic composition of embodiment 133 wherein the second GAS AI polypeptide is a second GAS AI-2 polypeptide.
- 136. The immunogenic composition of embodiment 133 wherein the second GAS AI 30 polypeptide is a second GAS AI-3 polypeptide.
 - 137. The immunogenic composition of embodiment 133 wherein the second GAS AI polypeptide is a second GAS AI-4 polypeptide.
 - 138. The immunogenic composition of embodiment 129 wherein the first GAS AI-1 polypeptide is selected from the group consisting of M6_Spy0157, M6_Spy0159, M6_Spy0160, CDC SS 410_fimbrial, ISS3650_fimbrial, DSM2071_fimbrial, and fragments thereof.
 - 139. The immunogenic composition of embodiment 130 wherein the first GAS AI-2 polypeptide is selected from the group consisting of GAS15, GAS16, GAS18, and fragments thereof.

polypeptide is selected from the group consisting of SpyM3_0098, SpyM3_0100, SpyM3_0102, SpyM3_0104, SPs0100, SPs0102, SPs0104, SPs0106, orf78, orf80, orf82, orf84, spyM18_0126, spyM18_0128, spyM18_0130, spyM18_0132, SpyoM01000156, SpyoM01000155, SpyoM01000154, SpyoM01000153, SpyoM01000152, SpyoM01000151, SpyoM01000150, SpyoM01000149, ISS3040_fimbrial, ISS3776_fimbrial, ISS4959_fimbrial, and fragments thereof.

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- 141. The immunogenic composition of embodiment 132 wherein the first GAS AI-4 polypeptide is selected from the group consisting of 19224134, 19224135, 19224137, 19224139, 19224141, 20010296_fimbrial, 20020069_fimbrial, CDC SS 635_fimbrial, ISS4883_fimbrial, ISS4538_fimbrial, and fragments thereof.
- 142. The immunogenic composition of embodiment 134 wherein the second GAS AI-1 polypeptide is selected from the group consisting of M6_Spy0157, M6_Spy0159, M6_Spy0160, CDC SS 410_fimbrial, ISS3650_fimbrial, DSM2071_fimbrial, and fragments thereof.
- 143. The immunogenic composition of embodiment 135 wherein the second GAS AI-2 polypeptide is selected from the group consisting of GAS15, GAS16, GAS18, and fragments thereof.
- 144. The immunogenic composition of embodiment 136 wherein the second GAS AI-3 polypeptide is selected from the group consisting of SpyM3_0098, SpyM3_0100, SpyM3_0102, SpyM3_0104, SPs0100, SPs0102, SPs0104, SPs0106, orf78, orf80, orf82, orf84, spyM18_0126, spyM18_0128, spyM18_0130, spyM18_0132, SpyoM01000156, SpyoM01000155, SpyoM01000154, SpyoM01000153, SpyoM01000152, SpyoM01000151, SpyoM01000150, SpyoM01000149, ISS3040_fimbrial, ISS3776_fimbrial, ISS4959_fimbrial, and fragments thereof.
- 145. The immunogenic composition of embodiment 137 wherein the second GAS AI-4 polypeptide is selected from the group consisting of 19224134, 19224135, 19224137, 19224139, 19224141, 20010296_fimbrial, 20020069_fimbrial, CDC SS 635_fimbrial, ISS4883_fimbrial, ISS4538 fimbrial, and fragments thereof.
- 146. The immunogenic composition of any one of embodiments 117-132 or 138-141 wherein the second Gram positive bacteria AI polypeptide is a Group B Streptococcus (GBS) AI polypeptide.
- 147. The immunogenic composition of embodiment 146 wherein the GBS AI polypeptide comprises a sortase substrate motif.
- 148. The immunogenic composition of embodiment 147 wherein the sortase substrate motif is an LPXTG motif.
- 149. The immunogenic composition of embodiment 148 wherein the LPXTG motif is represented by the amino acid sequence XPXTG, wherein the X at amino acid position 1 is an L, an I, or an F and the X at amino acid position 3 is any amino acid residue.
- 150. The immunogenic composition of embodiment 146 wherein the GBS AI polypeptide affects the ability of GBS bacteria to adhere to epithelial cells.
- 151. The immunogenic composition of embodiment 146 wherein the GBS AI polypeptide affects the ability of GBS bacteria to invade epithelial cells.

The immunogenic composition of embodiment 146 wherein the GBS AI polypeptide affects the ability of GBS bacteria to translocate through an epithelial cell layer.

- 153. The immunogenic composition of embodiment 146 wherein the GBS AI polypeptide is capable of associating with an epithelial cell surface.
- 154. The immunogenic composition of embodiment 146 wherein the associating with an epithelial cell surface is binding to the epithelial cell surface.

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- 155. The immunogenic composition of embodiment 146 wherein the GBS AI polypeptide is a full-length GBS AI protein.
- 156. The immunogenic composition of embodiment 146 wherein the GBS AI polypeptide is a fragment of a full-length GBS AI protein.
 - 157. The immunogenic composition of embodiment 156 wherein the fragment comprises at least 7 contiguous amino acid residues of the GBS AI protein.
 - 158. The immunogenic composition of embodiment 146 wherein the GBS AI polypeptide is a GBS AI-1 polypeptide.
 - 159. The immunogenic composition of embodiment 146 wherein the GBS AI polypeptide is a GBS AI-2 polypeptide.
 - 160. The immunogenic composition of embodiment 158 wherein the GBS AI-1 polypeptide is selected from the group consisting of GBS 80, GBS 104, GBS 52, and fragments thereof.
 - 161. The immunogenic composition of embodiment 159 wherein the GBS AI-2 polypeptide is selected from the group consisting of GBS 59, GBS 67, GBS 150, 01521, 01523, 01524, and fragments thereof.
 - 162. The immunogenic composition of any one of embodiments 117-132 or 138-141 wherein the second Gram positive bacteria AI polypeptide is a *Streptococcus pneumoniae* AI polypeptide.
 - 163. The immunogenic composition of embodiment 162 wherein the S. pneumoniae AI polypeptide comprises a sortase substrate motif.
 - 164. The immunogenic composition of embodiment 163 wherein the sortase substrate motif is an LPXTG motif.
 - 165. The immunogenic composition of embodiment 162 wherein the S. pneumoniae AI polypeptide affects the ability of S. pneumoniae to adhere to epithelial cells.
 - 166. The immunogenic composition of embodiment 162 S. pneumoniae AI polypeptide affects the ability of S. pneumoniae to invade epithelial cells.
 - 167. The immunogenic composition of embodiment 162 wherein the S. pneumoniae AI polypeptide affects the ability of S. pneumoniae to translocate through an epithelial cell layer.
 - 168. The immunogenic composition of embodiment 162 wherein the S. pneumoniae AI polypeptide is capable of associating with an epithelial cell surface.
 - 169. The immunogenic composition of embodiment 168 wherein the associating with an epithelial cell surface is binding to the epithelial cell surface.

polypeptide is a full-length S. pneumoniae AI protein.

- 171. The immunogenic composition of embodiment 162 wherein the S. pneumoniae AI polypeptide is a fragment of a full-length S. pneumoniae AI protein.
- 172. The immunogenic composition of embodiment 162 wherein the fragment comprises at least 7 contiguous amino acid residues of the *S. pneumoniae* AI protein.

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- 173. The immunogenic composition of embodiment 162 wherein the *S. pneumoniae* AI polypeptide is selected from the group consisting of SP0462, SP0463, SP0464, orf3_670, orf4_670, orf5_670, ORF3_14CSR, ORF4_14CSR, ORF5_14CSR, ORF3_19AH, ORF4_19AH, ORF5_19AH, ORF3_19FTW, ORF4_19FTW, ORF5_19FTW, ORF3_23FP, ORF4_23FP, ORF5_23FP, ORF3_23FTW, ORF4_23FTW, ORF5_23FTW, ORF3_6BF, ORF4_6BF, ORF5_6BF, ORF3_6BSP, ORF4_6BSP, ORF5_6BSP, ORF
- 174. The immunogenic composition of any one of embodiments 105-117 wherein the first Gram positive bacteria AI polypeptide is in oligomeric form.
- 175. The immunogenic composition of embodiment 174 wherein the oligomeric form is a hyperoligomer.
- 176. The immunogenic composition of embodiment 174 wherein the second Gram positive bacteria AI polypeptide is in oligomeric form.
- 177. The immunogenic composition of embodiment 176 wherein the oligomeric form is a hyperoligomer.
 - 178. The immunogenic composition of embodiment 176 wherein the first and the second Gram positive bacteria AI polypeptide are associated in a single oligomeric form.
 - 179. The immunogenic composition of embodiment 178 wherein the first and the second Gram positive bacteria AI polypeptide are chemically associated.
- 180. The immunogenic composition of embodiment 178 wherein the first and the second Gram positive bacteria AI polypeptide are physically associated.
- 181. The immunogenic composition of any one of embodiments 105-117 further comprising a Gram positive bacteria polypeptide not associated with an AI.
- 182. The immunogenic composition of embodiment 181 wherein the Gram positive bacteria polypeptide not associated with an AI is selected from the group consisting of GBS 322 and GBS 276.
- 183. The immunogenic composition of embodiment 182 wherein the Gram positive bacteria polypeptide not associated with an AI is GBS 322.
- 184. A modified Gram positive bacterium adapted to produce increased levels of AI surface protein.
- 185. The modified Gram positive bacterium of embodiment 184 wherein the AI surface protein is in oligomeric form.
- 186. The modified Gram positive bacterium of embodiment 185 wherein the oligomeric form is a hyperoligomer.

The modified Gram positive bacterium of any one of embodiments 184-186 which is a Group B Streptococcus bacterium.

- 188. The modified Gram positive bacterium of any one of embodiments 184-186 which is a Group A Streptococcus bacterium.
- 189. The modified Gram positive bacterium of any one of embodiments 184-186 which is a non-pathogenic Gram positive bacterium.

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- 190. The modified Gram positive bacterium of embodiment 189 wherein the non-pathogenic Gram positive bacterium is *Streptococus gordonii*.
- 191. The modified Gram positive bacterium of embodiment 189 wherein the non-pathogenic Gram positive bacterium is *Lactococcus lactis*.
 - 192. The modified Gram positive bacterium of any one of embodiments 184-186 which has been inactivated and wherein the AI surface protein is exposed on the surface of the Gram positive bacterium.
- 193. The modified Gram positive bacterium of any one of embodiments 184-186 which has been attenuated and wherein the AI surface protein is exposed on the surface of the Gram positive bacterium.
- 194. The modified GBS bacterium of embodiment 187 which has been inactivated and wherein the AI surface protein is exposed on the surface of the GBS bacterium.
- 195. The modified GBS bacterium of embodiment 187 which has been attenuated and wherein the AI surface protein is exposed on the surface of the GBS bacterium.
 - 196. The modified GAS bacterium of embodiment 188 which has been inactivated and wherein the AI surface protein is exposed on the surface of the GAS bacterium.
 - 197. The modified GAS bacterium of embodiment 188 which has been attenuated and wherein the AI surface protein is exposed on the surface of the GAS bacterium.
 - 198. The modified non-pathogenic bacterium of embodiment 189 which has been inactivated and wherein the AI surface protein is exposed on the surface of the non-pathogenic Gram positive bacterium.
 - 199. The modified non-pathogenic bacterium of embodiment 189 which has been attenuated and wherein the AI surface protein is exposed on the surface of the non-pathogenic Gram positive bacterium.
 - 200. A method for manufacturing an oligomeric adhesin island (AI) surface antigen comprising:

culturing a Gram positive bacterium that expresses an oligomeric AI surface antigen and isolating the expressed oligomeric AI surface antigen.

- 201. The method of embodiment 200 wherein the step of isolating is performed by collecting said oligomeric AI surface antigen from Gram positive bacterium secretions in the Gram positive bacterium culture.
 - 202. The method of embodiment 200 further comprising a step of purifying.

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The method of embodiment 202 wherein the oligomeric AI surface antigen is purified from the Gram positive bacterium cell surface.

- 204. The method of embodiment 200 wherein the Gram positive bacterium is adapted for increased AI protein expression.
- 205. The method of any one of embodiments 200-204 wherein the Gram positive bacterium is a Group A Streptococcus bacterium.

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- 206. The method of any one of embodiments 200-204 wherein the Gram positive bacterium is a Group B Streptococcus bacterium.
- 207. The method of any one of embodiments 200-204 wherein the oligomeric AI surface antigen is in hyperoligomeric form.
 - 208. The method of embodiment 200 wherein the Gram positive bacterium expresses the oligomeric AI surface antigen recombinantly.
 - 209. The method of embodiment 208 wherein the Gram positive bacterium further manipulated expresses at least 1 AI sortase.
- 210. The modified Gram positive bacterium of any one of embodiments 184-186 which is a S. pneumoniae bacterium.
 - 211. The method of any one of embodiments 200-204 wherein the Gram positive bacterium is S. pneumoniae.

1. An immunogenic composition comprising a purified Group B Streptococcus (GBS) adhesin island (AI) polypeptide in oligomeric form.

2. The immunogenic composition of claim 1 wherein the GBS AI polypeptide is selected from a GBS AI-1.

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- 3. The immunogenic composition of claim 1 wherein the GBS AI polypeptide is selected from a GBS AI-2.
- 4. The immunogenic composition of claim 2 wherein the GBS AI polypeptide is selected from the group consisting of GBS 80, GBS 104, GBS 52, and fragments thereof.
- 5. The immunogenic composition of claim 3 wherein the GBS AI polypeptide is selected from the group consisting of GBS 59, GBS 67, GBS 150, 01521, 01523, 01524, and fragments thereof.
 - 6. The immunogenic composition of claim 4 wherein the GBS AI polypeptide is GBS 80.
- 7. The immunogenic composition of any of claims 1-6 wherein the oligomeric form is a hyperoligomer.
 - 8 (22). An immunogenic composition comprising a purified Gram positive bacteria adhesin island (AI) polypeptide in an oligomeric form.
 - 9 (23). The immunogenic composition of claim 8 wherein the Gram positive bacteria is of a genus selected from the group consisting of *Streptococcus*, *Enterococcus*, *Staphylococcus*, *Clostridium*, *Corynebacterium*, or *Listeria*.
 - 10 (24). The immunogenic composition of claim 9 wherein the Gram positive bacteria is of the genus *Streptococcus*.
 - 11 (35). The immunogenic composition of claim 10 wherein the genus *Streptococcus* bacteria is Group A Streptococcus (GAS) bacteria and the Gram positive bacteria AI polypeptide is a GAS AI polypeptide.
 - 12 (36). The immunogenic composition of claim 11 wherein the GAS AI polypeptide is selected from a GAS AI-1.
 - 13 (37). The immunogenic composition of claim 11 wherein the GAS AI polypeptide is selected from a GAS AI-2.
 - 14 (38). The immunogenic composition of claim 11 wherein the GAS AI polypeptide is selected from a GAS AI-3.
 - 15 (39). The immunogenic composition of claim 11 wherein the GAS AI polypeptide is selected from a GAS AI-4.
- 16 (66). The immunogenic composition of any one of claims 8-15 wherein the oligomeric form is a hyperoligomer.
 - 17. An immunogenic composition comprising a first and a second Group B Streptococcus (GBS) adhesin island (AI) polypeptide.

18. The immunogenic composition of claim 17 wherein the first GBS AI polypeptide is encoded by a GBS AI-1.

- 19. The immunogenic composition of claim 18 wherein the second GBS AI polypeptide is encoded by a GBS AI-2.
- 20. The immunogenic composition of claim 18 wherein the first GBS AI polypeptide is selected from the group consisting of GBS 80, GBS 104, GBS 52, and fragments thereof.

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- 21. The immunogenic composition of claim 19 wherein the second GBS AI polypeptide is selected from the group consisting of GBS 59, GBS 67, GBS 150, 01521, 01523, 01524, and fragments thereof, and wherein the first and the second GBS AI polypeptide are not the same polypeptide.
- 22. The immunogenic composition of claim 19 wherein the first GBS AI polypeptide is GBS 80 and the second GBS AI polypeptide is GBS 67.
- 23. An immunogenic composition comprising a first and a second Gram positive bacteria adhesin island (AI) polypeptide.
- 24. The immunogenic composition of claim 23 wherein the Gram positive bacteria is Streptococcus, Enterococcus, Staphylococcus, Clostridium, Corynebacterium, or Listeria.
- 25. The immunogenic composition of claim 23 wherein the first Gram positive bacteria AI polypeptide is a first Group A Streptococcus (GAS) AI polypeptide.
- 26. The immunogenic composition of claim 25 wherein the first GAS AI polypeptide is a first GAS AI-1 polypeptide.
- 27. The immunogenic composition of claim 25 wherein the first GAS AI polypeptide is a first GAS AI-2 polypeptide.
- 28. The immunogenic composition of claim 25 wherein the first GAS AI polypeptide is a first GAS AI-3 polypeptide.
- 29. The immunogenic composition of claim 25 wherein the first GAS AI polypeptide is a first GAS AI-4 polypeptide.
- 30. The immunogenic composition of any one of claims 25-29 wherein the second Gram positive bacteria AI polypeptide is a second GAS AI polypeptide.
- 31. The immunogenic composition of claim 30 wherein the second GAS AI polypeptide is a second GAS AI-1 polypeptide.
 - 32. The immunogenic composition of claim 30 wherein the second GAS AI polypeptide is a second GAS AI-2 polypeptide.
 - 33. The immunogenic composition of claim 30 wherein the second GAS AI polypeptide is a second GAS AI-3 polypeptide.
- 34. The immunogenic composition of claim 30 wherein the second GAS AI polypeptide is a second GAS AI-4 polypeptide.
- 35. A modified Gram positive bacterium adapted to produce increased levels of AI surface protein.

36. The modified Gram positive bacterium of claim 35 wherein the AI surface protein is in oligomeric form.

- 37. The modified Gram positive bacterium of claim 36 wherein the oligomeric form is a hyperoligomer.
- 38. The modified Gram positive bacterium of any one of claims 35-37 which is a nonpathogenic Gram positive bacterium.

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- 39. The modified Gram positive bacterium of claim 38 wherein the non-pathogenic Gram positive bacterium is Lactococcus lactis.
- A method for manufacturing an oligomeric adhesin island (AI) surface antigen 10 comprising:

culturing a Gram positive bacterium that expresses an oligomeric AI surface antigen and isolating the expressed oligomeric AI surface antigen.

FIGURE 1: Adhesion Island 1

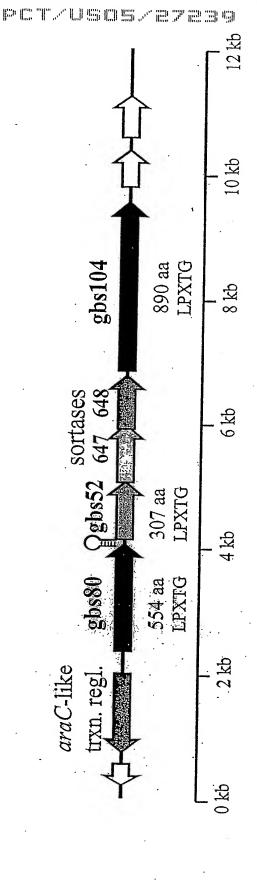


Figure 2: Conservation of AI-1 in GBS serotypes and strain isolates

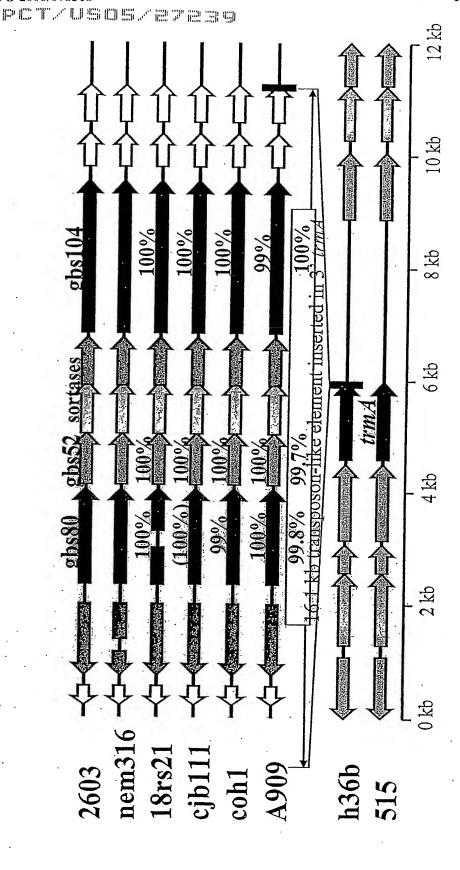
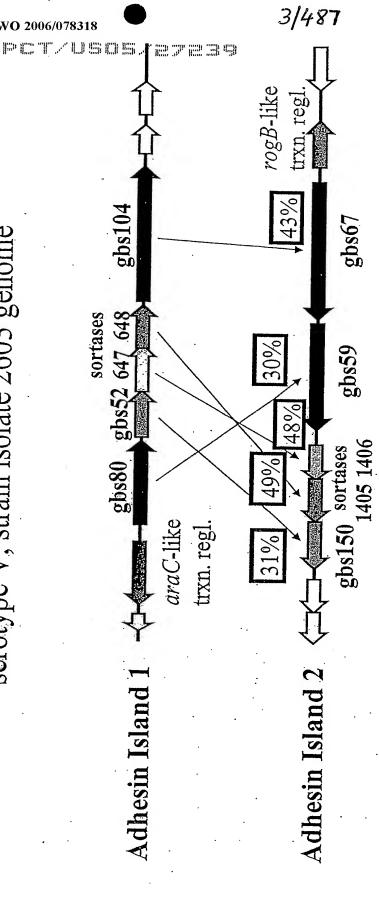
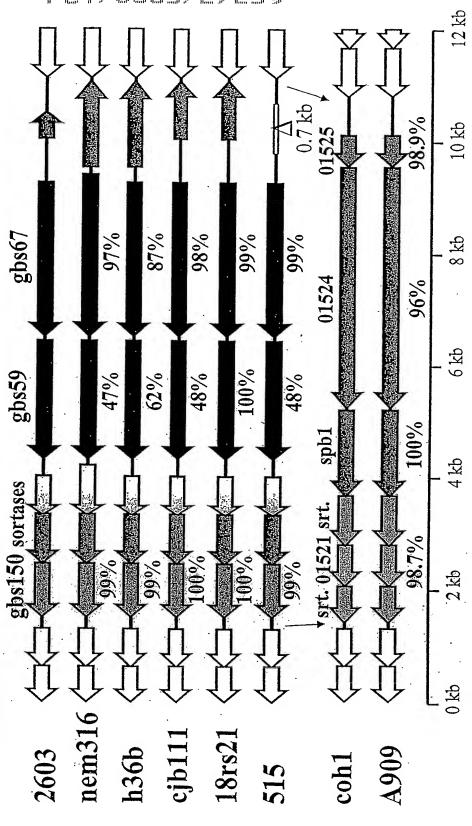


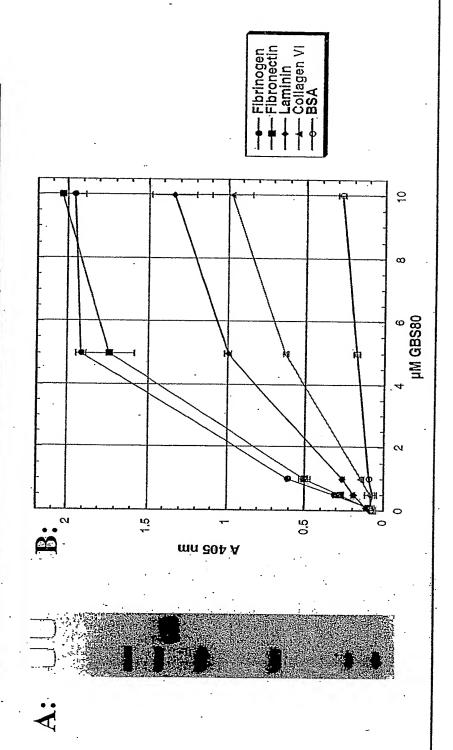
FIGURE 3: Correlation of AI-1 and AI-2 within GBS serotype V, strain isolate 2603 genome

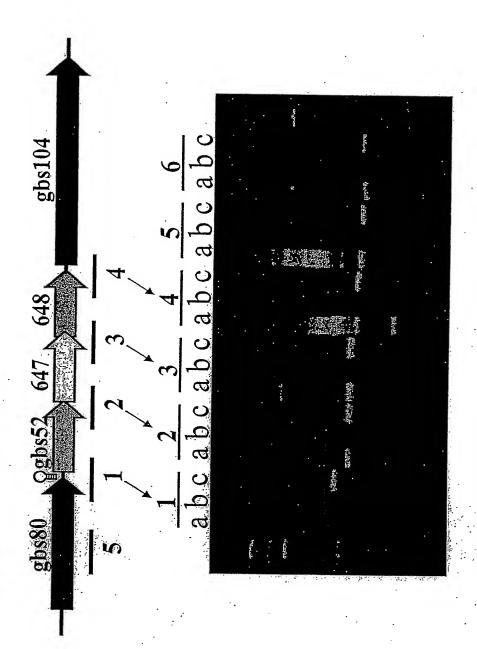




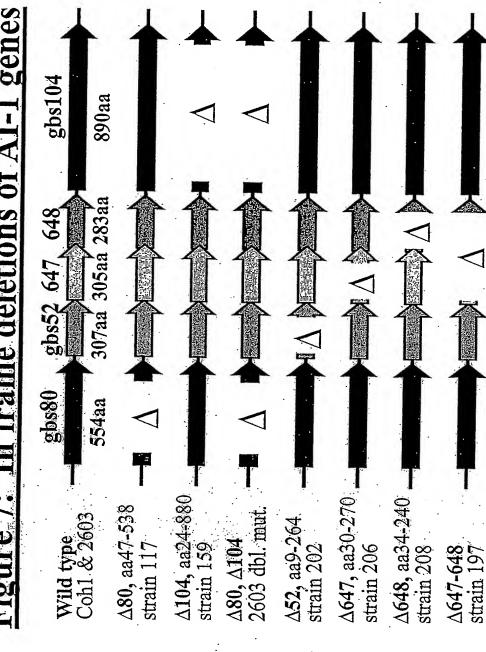
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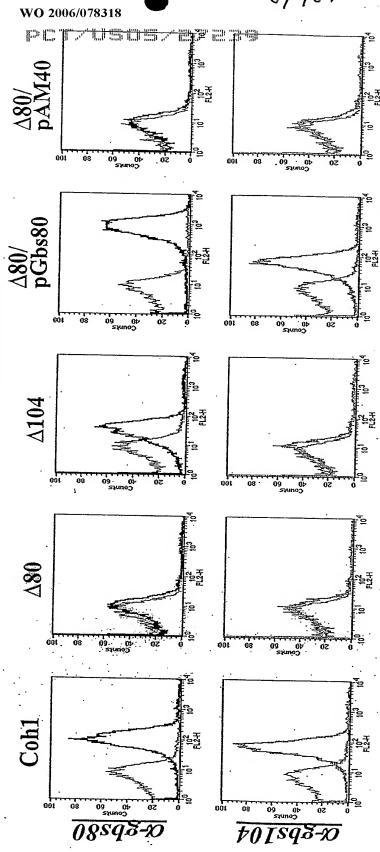
Figure 5: Purified gbs80 protein binds fibronectin and fibrinogen in an ELISA



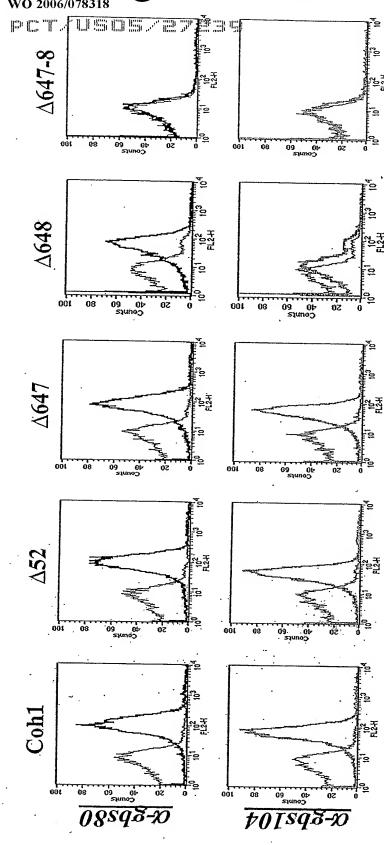




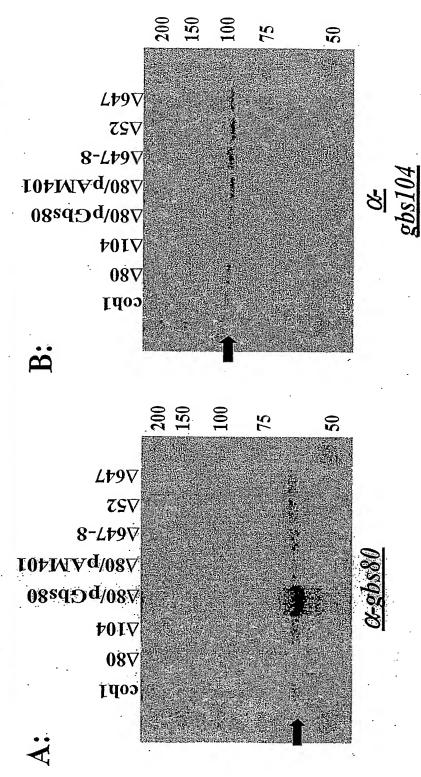


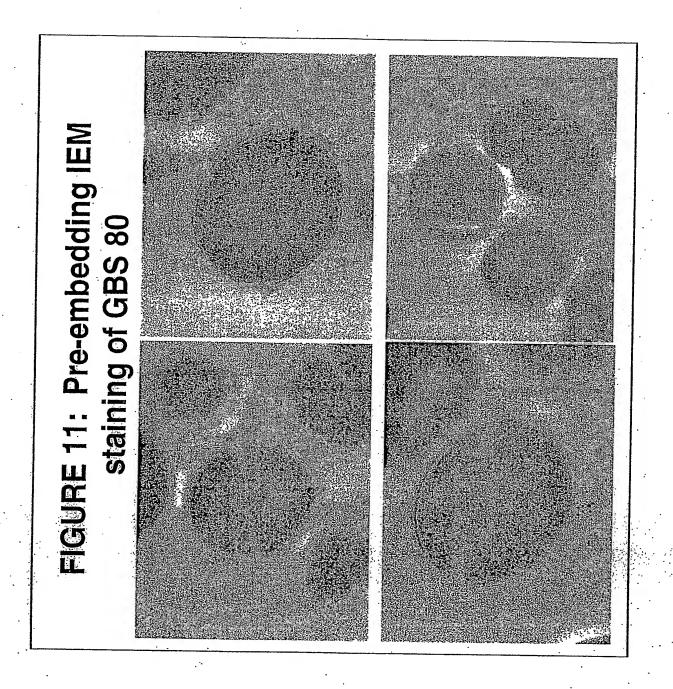






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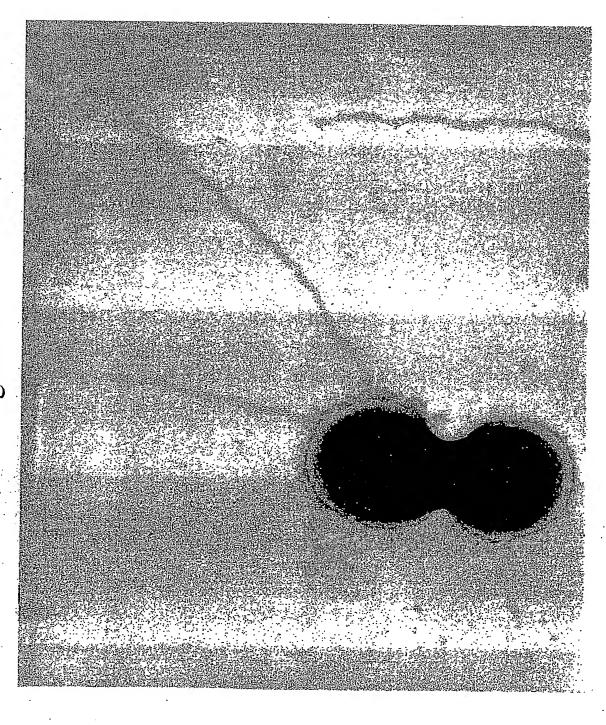


PHD SECONDARY STRUCTURE PREDICTION for GBS 067

FIGURE 12: Predicted Secondary Structure for GBS 067

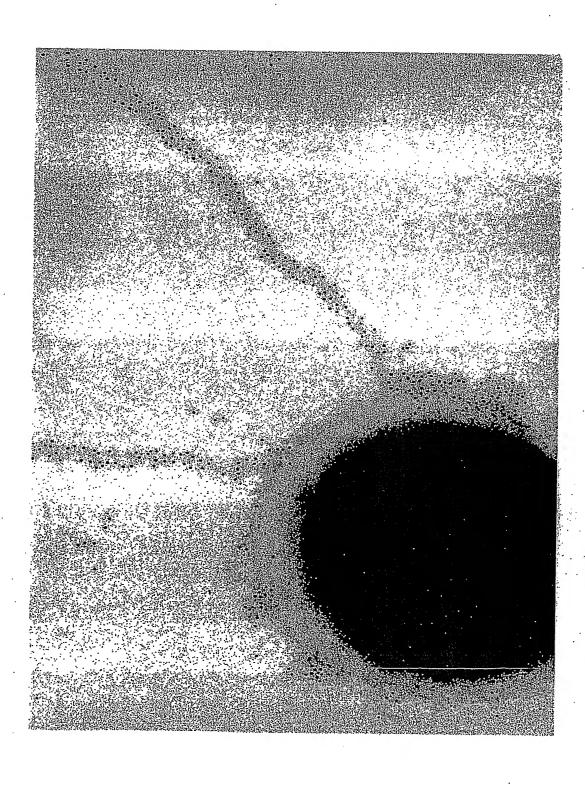
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09.	KATFVLKTTA CCBEBEBECC SDKNSTIGON	OCCCCCCCCC RISEVGDLAH	KDILGANSDN	TEAPKAKWGS'	NFKLGASYES :ecccccchH	YPKGTIYRNG	CEITELMRS	CONHUNINA OTLOPSDYTL	SCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC	ceeeecCCC(PELOBENED' "huuruhabh	KNI IAVNKO:	hhhhhhhhhHH Astro	CecCC		
ςς 0	CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC	SCOPEEEECK KEIPEGTLSKI SCCCCCCCC	СААБАГ. ОННИННИНН	АВЕТТККІРІ ІННННННЬСС	WETRSYAIN CCCccceeco	CHYLDLNLN	TKEEAFKLSI	HHHHHHCCC XINLQLGNG(PYDVKI,DDSE	BEEeccCC	NNKLLLKGAT	LTFEVVKGS	MEEEEcccc1	MECCCCCCCCC		
·40 -	GAKĞKLVVKR CCCCEEEEE NQTWQVKVES	CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC	NFORHNKAKE CCCChhihi	NYSHKOLTNN CCcchhhhh	OKIIVHVTDC Cebebebecc	TOITSGNLOR ENDEECCCCC	KKNØDGTFOK	SCCCCCRARE NGTIEDPMGD	eeeEecccc NIGEGOKVTI	CCCCCEEE	ETEPTKVDKE SPEPFOCC	DYOKITNKPI	MANTAGGTYT	Coeccicee		
30	MRKYQKFSKILTLSLFCLSQIPLNTNVLGESTVERNGAKGKLVVKKTDDQNKPLSKATFVLKTTAHPESK Coccucceeeeebbegeeebbcocccccccccccccccccccccc	hHHHNNNeeBeeecCCCCCCCCCCCCCCCCCCCCCCCEBBBBBBBCCCCEBBBBCCCCCC	ELTVSGKTIVKPVDKOKPLDVVFVLDNSNSMANDGFNFORHNKAKKAAEALGTAVKDILGANSDNRVALV EBECCCCEEEECCCCCCCCEEEEEECCCCCCCCCCCCC	TYGSDIFDGRSVDVVKGFKEDDKYYGLOTKFITGGENYSHKOLTNNAEELIKRIPTEAPKAKWGSTTNGL EcceeecCCCeebbecceecCCCcaeeebbbbbecccchhhhhhhhhhhhhhccccccccccc	TPBQQKEYYLSKVGETFTWKAFMEADDILSOWNRNSOKIIVHVTDGVPTRSYAINNFKLGASYBSQFBQM Ccccccebebeccccchhhhhhhhhhhhhhhhhhh	KKNGYLNKSNFLLTDKPEDIKGNGESYFLRPTDSKOTOIISGNLOKLHYLDLNLNYPKGTIYRNGPVKEH HHACCCCCCeeeecCCCCCCCCCEBBGEECCOGEEBBEECCCCCCCEEECCCCCCCCCEECCCCC	GTPTKLYINSLKOKNYDIFNFGIDISGFRÓVNNBERKKNÓDGTFOKLKEBAFKLSDGELTELMRSFSSKP	CCCCERERACCOCCCCCCCCCCCCCCCCCCCCCCCCCCCC	CCEEBEBECCCCCCHHHHHHHHHHHHHHHHHHHBBCCGGGEGECCCCCEBECCCCCCCCCC	DOCCOCCCCCCCCCCeeeeeecDDDDCCCCEEEEEEEEEEEEECCCCCCCCEEEEEEEEECCCCCC	NPKSEDPNTLRDFPIPKIRDVREYPTTTIKWEKKAGEIEFIKVDKDNNKLLLKGATFELQEFWEDYKLYL COCOCOCOCOCOCOCOCOCOCA を発展を表するである。	PIKNNNSKVVTGENGKISYKDEKDGKYQE, TEAVSERD KOKITNKPILTFEVVKGSIKNIIAVNKQISEYH	eecCCCCcвввсcCCcвeввecccCcвв <u>ррабобою</u> рнийссссввввесоосирииннинни вваркниттипнтрркаттрипоскатьзятата	HACCCERRECCCCCCCERECCCCCCERRECCCCCCCCCCC		
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10	SKILTLSLFC eeeeeEEece LTGEATFDNI	eeEeeeocCC IYEDTKESYK ceecCcccc	TIVKPVDKOR	DGRSVDVVKO CCCeeBBecc	YYLSKVGETE BEBeaccaat	KSNFLLTDKE CGEEECCCC	INSLKOKNYĽ	ercccccc TSADTSNNĖI	eecCCCcHHH ATGGPNNDGC	مدددددددد	NTLRDFPLFR	KVVTGENGKI	CEEECCCCCE ITNTHIPPKG	Beccccccc	e length";	
	MRKYQKF Coccocc IEKVTAE	NAMHNNA KQYPPTG CCCCC	ELTVSGK	TYGSDIF	TPEQQKE	KKNGYLN HHhCCcc	GTPTKLY	EYYTPIV	CCCCEEEE	CCCCCCCC	NPKSEDPI	PIKNNNSI	BEGDKHL.	HhCCceE	Sequence	· OHO

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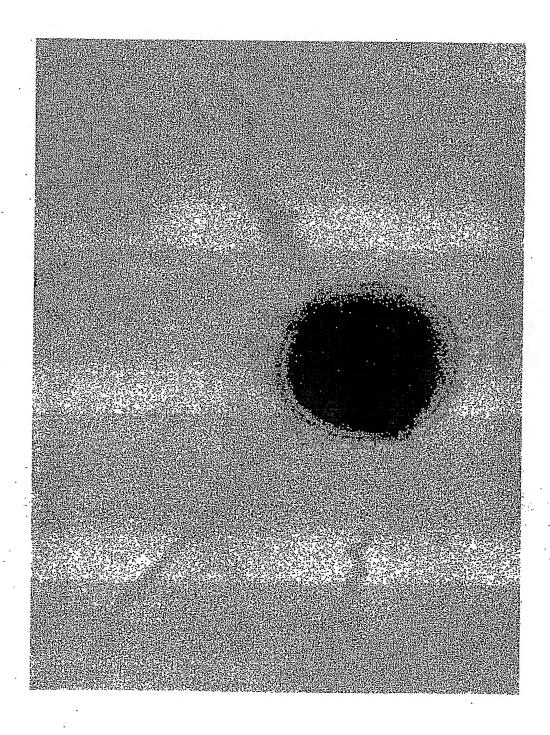


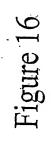
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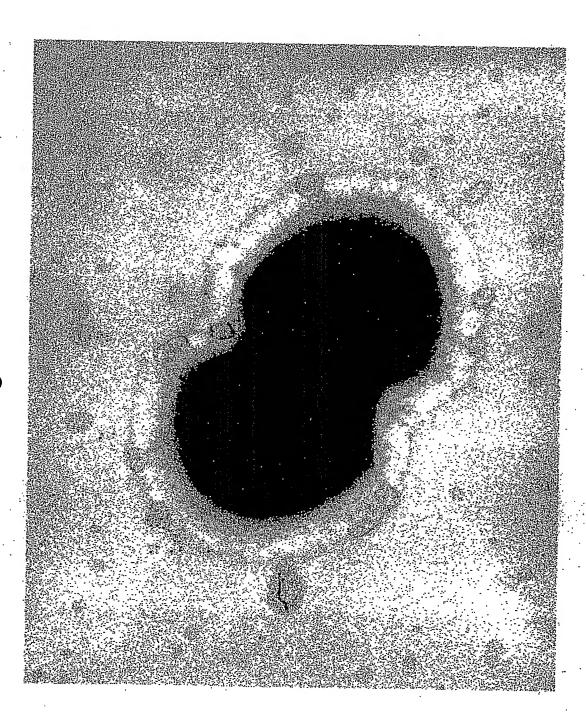
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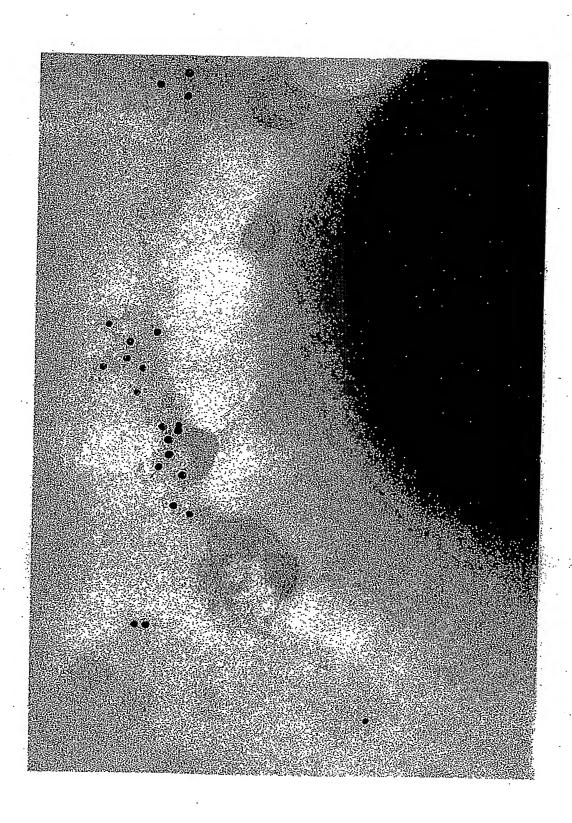
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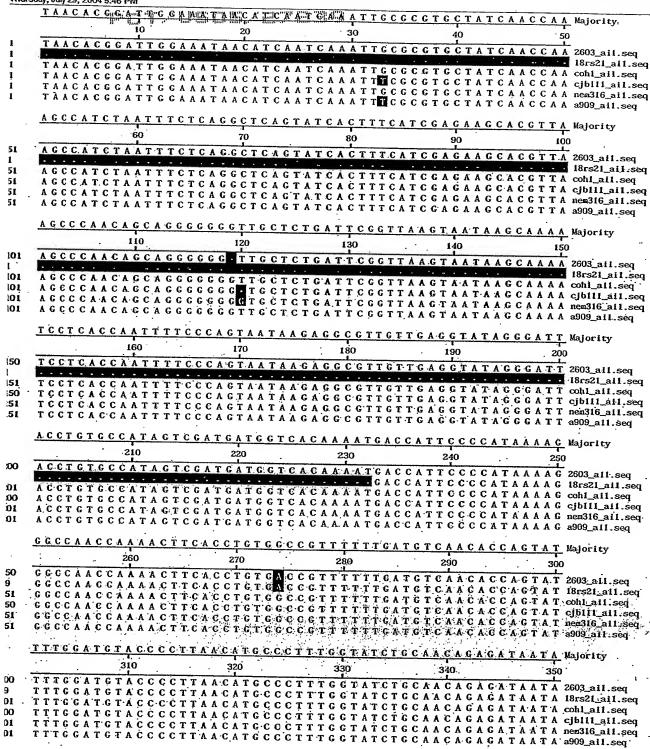












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WO 2006/078318

Alignment Report of Al-1_alignment, using J. Hein method with Weighted residue weight table. Thursday, July 29, 2004 5;46 P.M. ... AAT COACAATACTACATTTGCTCCTC Majority AGGTGGTTCTCCAC 1060 1070 1080 1090 1100 AGGTGGTTGTCCACATAATGGAGAATACTATTGTACATTTGCTGCTGCTTGTC 2603_ai1.seq. 1050 A G G T G G T T G T C C A C A T A A T G G A C A A T A C T A T T G T A C A T T T G C T G C T T G T C 18rs21_ai1.seq 819 A G G T G G T T G T C C A C A T A A T G G A G A A T A C T A T T G T A C A T T T G C T G C T T G T C cohl_ail.seq 1051 A G G T G C T T G T C C A C A T A A T G G A G A A T A C T A T T G T A C A T T T G C T G C T T G T C cjbili_ail.seq A G G T G G T T G T C C A C A T A A T G G A G A A T A C T A T T G T A C A T T T G C T G C T T G T C nem316_ai1.seq A G G T C G T C C C A C A T A A T G G A G A A T A C T A T T G T A C A T T T G C T G C T T G T C a 909_ail.seq A G A G A T G C T C T T A T T C G T T A A G G A T T C T G A A A A T C A A T A A G A G C T G C A C Majority 1110 1130 1140 1150 A G.A G A T G C T C T T A T T G G T T A A G G A T T C T G A A A A A T C A A T A A G A G C T G C A C 2603_ail.seq 1100 A GA GA T G C T C T T A T T G G T T A A G G A T T C T G A A A A A T C A A T A A G A G C T G C A C 18rs21_ai1.seq A G A G A T G C T C T T A T T G G T T A A G G A T T C T G A A A A A T C A A T A A G A G C T G C A C cohl_ail.seq 1101 A G A G A T G C T C T T A T T G C T T A A G G A T T C T G A A A A A T C A A T A A G A G C T G C A C cjbiii_ail.seq A G A G A T G C T C T T A T T G G T T A A G G A T T C T G A A A A A T C A A T A A G A G C T G C A C nem316_ai1.seq 1101 A G A G A T G C T C T T A T T G G T T A A G G A T T C T G A A A A A T C A A T A A G A G C T G C A C a909_ail.seq A G.C. G.A.A.T. C. T.T. G.A.A.A. C.A.T. C.A.G.A.T. C.A.G.G.A.G.C.C.T.C.T.T.C.G.T.T.T.A.A.G.C.C. Majority 1170 1160 1180 1190 1200 1150 A G C G A A T T C T T G A A A C A T C A A T A A G A T C A G G A G C C T C T T C G T T T A A A G C C 2603_ail.seq 319 A.G.C.G.A.A.T.C.T.T.G.A.A.A.C.A.T.C.A.G.A.T.C.A.G.G.A.G.C.C.T.C.T.T.C.G.T.T.T.A.A.G.C.C. 18rs21_ail.seq 1151 A G C G A A T T C T T G A A A C A T C A A T A A G A T C A G G A G C C T C T T C G T T T A A A G C C conlail.seq 1150 A G C G A A T T C T T G A A A C A T C A A T A A G A T C A G G A G C C T C T T C G T T T A A A G C C cjbili_aii.seq A G C G A A T T C T T G A A A C A T C A A T A A G A T C A G C A G C C T T T T C G T T T A A A G C C nem316 ail.seq 1151 A G C G A A T T C T T G A A A C A T C A A T A A G A T C A G G A G C C T C T T C G T T T A A A G C C a909_ail.seq 1151 A T A T A G T G C T T T A C C A G C G C A T A A C T T T T A G C C A C A T C A G T A T T T T C C T C Majority 1210 1220 1230 . 1240 1250 ATATAGTGCTTTACCAGCGCATAACTTTTAGCCACATCAGTATTTTCCTC 2603_ail.seq 1200 A TATAGT G C TTT A C C A G C G C A T A A C T T T T A G C C A C A T C A G T A T T T T C C T C 18rs21_ai1.seq 169 ATATAGT GCTTTACCAGCGCATAACTTTTAGCCACATCAGTATTTTCCTC contail.seq 201 1200 ATATAGTGCTTTACCAGCGCATAACTTTTAGCCAATCAGTATTTTTCTC cjbli1_ail.seq ATATAGTGCTTTACCAGCGCATAACTTTTAGCCAACATCAGTATTTTCCTC nem316_ail.seq 1201 igo i ATATAGTGCTTTACCAGCGCATAACTTTTAGCCAATCAGTATTTTCCTC a909_ai1.seq GAAACTTAATTCTAGTAATTTTGTTAAGTAAACAACAGTTAAGTTCTTT Majority 1260 1270 1280 1290 1300 GAAACTTAATTCTAGTAATTTTGTTAAGTAAACAACAGTTAAGTTCTTTT 2603_ail.seq GAAACTTAATTCTAGTAATTTTGTTAAGTAAACAACAGTTAAGTTCTTTT 18rs21_a11.seq .019 GAAACTTAATTCTAGTAATTTTGTTAAGTAAACAACAGTTAAGTTCTTTT cohlail.seq GAAACTTAATTCTAGTAATTTTGTTAAGTAAACAACAGTTAAGTTCTTTT cjbiil_ail.seq GAAACTTAATTCTAGTAATTTTGTTAAGTAAACAACAGTTAAGTTCTTTT nem316_ail.seq GAAACTTAATTCTAGTAATTTTGTTAAGTAAACAACAGTTAAGTTCTTTT a909_ai1.seq C A G C T C T T A G G G C A G G G A T T G A A G A T G A GGTAACACTGGATGATGGGAGG Majority 1310 1320 1330 .1340 1350 CAGCTCTTAGGGCAGGGATTGAAGATGAGGTAACACTGGATGATGGCAGG 2603 ail seq CAGCTCTTAGGGCAGGATTGAAGATGAGGTAACACTGGATGATGGGAGG 18rs21 ail seq CAGCTCTTAGGGGCAGGGATTGAAGATGAGGTAACACTGGATGATGGGAGG cohlail seq 300 069 301 CAGCTCTTAGGGCAGGGATTGAAGATGAGGTAACACTGGATGGTGGGGAGGGBHTakkseq 300 CACCTCTTAGGGCAGGATTGAAGATGAGGTAACACTGGGATGATGGGAAGG nem316 all seq 301 C G A T T A A T T T C T T G C T T T A A C A G T T G A G T G T T A C C C A G C T T A A C G A G A T C Majority 1360 1370 1390 1380 . C G A T T A A T T T C T T G C T T T A A C A G T T G A G T G T T A C C C A G C T T A A C G A G A T C 2603_ail.seq 350 CGATTAATTTCTTGCTTTAACACTTGAGTGTTACCCAGCTTAACGAGATC 18rs21_a11.seq 119 C G A T T A A T T T C T T G C T T T A A C A G T T G A G T G T T A C C C A G C T T A A C G A G A T C cohi_all.seq C G A T T A A T T T C T T G C T T T A A C A G T T G A G T G T T A C C C A G C T T A A C G A G A T C. cjbiii_aii.seq C.G.A.T.T.A.A.T.T.C.T.T.G.C.T.T.T.A.A.C.A.G.T.T.G.A.G.T.G.T.T.A.C.C.C.A.G.C.T.T.A.A.C.G.A.G.A.T.C. nem316_ai1.seq

C G A T T A A T T T C T T G C T T T A A C A G T T G A G T G T T A C C C A G C T T A A C G A G A T C a909_a11.seq

m WO~2006/078318hursday, July 29, 2004 5:46 PM AATAATGTGATTGAATTT Majority 1420 1430 1440 AATAATGTGATTGAGATGGTTTAAAAACAGTGGGTAACTGAAAAGAGTTTT 2603_ail.seq 400 AATAATGTGATTGAGATGGTTTAAAACAGTGGGTAACTGAAAAGAGTTTT 18rs21_ai1.seq 169 AATAATGTGATTGAGATGGTTTAAAACAGTGGGTAACTGAAAAGAGTTTT cohl_ail.seq 401 AATAATGTGATTGAGATGGTTTAAAACACTGGGTAACTGAAAAGAGTTTT cjb111_ai1.seq 400 AATAATGTGATTGAGATGGTTTAAAACAGTGGGTAACTGAAAAGAGTTTT nem316_ail.seq 401 AATAATGTGATTGAGATGGTTTAAAACAGTGGGTAACTGAAAAGAGTTTT a909_all.seq 401 TCTTAGTATGTTTTAGGTGAAGAACAATATCAGGATCCGCAACAATCTGT Majority 1470 1480 1490 TCTTAGTATGTTTTAGGTGAAGAACAATATCAGGATCCGCAACAATCTGT 2603_ai1.seq 450 TCTTAGTATGTTTAGGTGAAGAACAATATCAGGATCCGCAACAATCTGT 18rs21_ail.seq 219 TCTTAGTATGTTTTAGGTGAAGAACAATATCAGGATCCGCAACAATCTGT coh1_ai1.seq 451 TCTTAGTATGTTTAGGTGAAGAACAATATCAGGATCCGCAACAATCTGT cjb111_ai1.seq 450 TCTTAGTATGTTTAGGTGAAGAACAATATCAGGATCCGCAACAATCTGT nex316_ail.seq 451 TCTTAGTATGTTTAGGTGAAGAACAATATCAGGATCCCCCAACAATCTGT a909_ail.seq 451 TCTGACTCTTCTAATAAATGATTGATGGCTTGTTGGCAACTAGCCTCAAA Wajority 1510 1520 1530 1540 1550 TCTGACTCTTCTAATAAATGATTGATGACTTGTTGGCAACTAGCCTCAAA 2603_ai1.seq 500 TCTGACTCTTCTAATAAATGATTGATGACTTGTTGGCAACTAGCCTCAAA 18rs21_ai1.seq 269 501 TCTGACTCTTCTAATAAATGATTGATGGCTTGTTGGCAACTAGCCTCAAA cjb111_a11.seq 500 TCTGACTCTTCTAATAAATGATTGATCCCTTGTTGGCAACTAGCCTCAAA niem316_ai1.seq 501 TCTGACTCTTAATAAATGATTGATGGCTTGTTGGCAACTAGCCTCAAA a909_ail.seq 501 CTGTGTTTGGAAAAGGCATCGATAGACAAGAAGACTACGTATACTGG Majority 1560 1570 1580 1590 1600 CTGTGTTTGGAAAAAGGCATCGATAGACACAAAGAAGACTACGTATACTGG 2603_all.seq CTGTGTTTGGAAAAAGGCATCGATAGACACAAGAAGACTACGTATACTGG 18rs21_ail.seq 550 319 CTGTGTTTGGAAAAGGCATCGATAGACACAAGAGACTACGTATACTGG cohl_ai1.seq 551 CTGTGTTTGGAAAAGGCATCGATAGACACAAGAAGACTACGTATACTGG cjbili_aii.seq 550 CTGTGTTTGGAAAAAGGCATCGATAGACAAGAAGACTACGTATACTGG nem316_ai1.seq 551 CTGTGTTTGGAAAAAGGCATCGATAGACACAAGAAGACTACGTATACTGG a909_ai1.seq TAGTAGGAAAACAAGGGACAAGCTTTATAGGATAAGATTTCTTTTTA Majority 1610 1620 1630 1640 TAGTAGGAAAACAAGGGACAAGCTTTATAGGATAAGATTTCTTTTTA 2603_aii.seq TAGTAGGAAAACAAGGGACAAGCTTTATATAGGATAAGATTTCTTTTTTA 18rs21_ail.seq TAGTAGGAAAACAAGGGACAAGCTTTATAGGATAAGATTTCTTTTTA cohl_ail.seq 100 TAGTAGGAAAACAAGGGACAAGCTTTATATAGGATAAGATTTCTTTTTA cjbli1_ail.seq 900 TAGTAGGAAAACAAGGGACAAGCTTTATATAGGATAAGATTTCTTTTTA nem316_ai1.seq. Ю1 TAGTAGGAAAACAAGGGACAAGCTTTATATAGGATAAGATTTCTTTTTA a909_ail.seq. CTACGATGAGAAAATTGTTCTAGAAAGCGACTGGATAACTGTTCTTGCCT 1660 1670 1680 1690 . : 1700 150 TTACGATGAGAAAATTGTTCTAGAAAGCGACTGGATAACTGTTCTTGCCT 2603_ail.seq 119 CTACGATGAGAAAATTGTTCTAGAAAAGCGACTGGATAACTGTTCTTGCCT 18rs21_ail.seq CTACGATGAGAAAATTGTTCTAGAAAGCGACTGGATAACTGTTCTTGCCT cohlaii.seq CTACGATGAGAAATTGTTCTAGAAAGCGACTGGATAACTGTTCTTGCCTTGGATASeq 51 ATTGATATCAGGGGTATAGGGATAAAATGGTCCAATAAGAATAAGATAAGATAAGATAAGGA 1710 1720 . 1730 1740 1750 ATTGATATCAGGGCTATAGGGATAAAATGGTCCAATAGGATAAGATAGGATATT 2603_ai1.seq ATTGATATCAGGGCTATAGGGATAAATGGTCCAATAGCAATAAGATATT 18rs21_a11.seq 69 10 ATT GATAT CAG G G CTATA G G G ATAAAAT G G T C C AATA G C AATAA G ATAT cohi_ail.seq ATTGATATCAGGGCTATAGGGATAAAATGGTCCAATAGCAATAAGATATT cjbiii_aii.seq '00 ATTGATATCAGGGGTATAGGGATAAATGGTCCAATAGCAATAAGATATT nem316_all.seq. ATTGATATCAGGGCTATAGGGATAAAATGGTCCAATAGCATAAGATA TT a909_a11.seq

hursday, July 29, 2004 5:46 PM AATTAAAGAATCTTCAAAAAGACCCTCATAAACA Majority CACACACA"C G"AA'A 1760 1770 1780 1790 GACAGACAGGAAAAATTAAGAATGATTCTTCAAAAAGACCCTCATAAACA 2603_ai1.seq 750 GACAGACAGGAAAATTAAGAATGATTCTTCAAAAAGACCCTGATAAACA 18rs21_ai1.seq 519 GACAGACAGGAAAATTAAGAATGATTCTTCAAAAAGACCCTCATAAACA cohl_all.seq 751 GACAGACAGGAAAATTAAGAATGATTCTTCAAAAAGACCCTCATAAACA cjbii1_ai1.seq 750 GACAGACAGGAAAATTAAGAATGATTCTTCAAAAAGA<u>C</u>CCTCATAAACA nem316_ai1.seq 751 GACAGACAGGAAAATTAAGAATGATTCTTCAAAAAGAAACATAAACA a909_ai1.seq 751 GTGATATCTTGGTTATAAGGGATAGCTAAATGTTTTAAAAAACTGATAGTA Majority 1810 1820 1830 1840 1850 CTGATATCTTGGTTATAAGGGATAGCTAAATGTTTTAAAAACTGATAGTA 2603_ai1.seq 800 GTGATATCTTGGTTATAAGGGÄTAGCTAAATGTTTTAAAAACTGATAGTA 18rs21_ai1.seq 569 GTGATATCTTGGTTATAAGGGATAGCTAAATGTTTTAAAAACTGATAGTA cohl_ail.seq 801 GTGATATCTTGGTTATAAGGGATAGCTAAATGTTTTAAAAACTGATAGTA cjbiil_ail.seq ROO GTGATATCTTGGTTATAAGGGATAGCTAAATGTTTTAAAAACTGATAGTA nem316_ail.seq 801 GTGATATCTTGGTTATAAGGGATAGCTAAATGTTTTAAAAACTGATAGTA a909_ai1.seq 801 A G G C A A C A G A T A G T C T T C G T T A C C A T A T A A C T G A A C G A G T T C C T T G T C T C Wajority 1860 1870 1880 1890 1900 AGGCAACAGATAGTCTTCGTTACCATATAACTGAACGAGTTCCTTGTCTC 2603_ai1.seq 850 AGGCAACAGATAGTCTTCGTTACCATATAACTGAACGAGTTCCTTGTCTC 18rs2f_ail.seq 619 AGGCAACAGATAGTCTTCGTTACMATAACTGAACGAGTTCCTTGTCTC cohl all.seq 851 A G G C A A C A G A T A G T C T T C G T T A C C A T A T A A C T G A A C G A G T T C C T T G T C T C cjbli1_ail.seq 850 A G G C A A C A G A T A G T C T T C G T T A C C A T A T A A C T G A A C G A G T T C C T T G T C T C nem316_ai1.seq A G G C A A C A G A T A G T C T T C G T T A C C A T A T A A C T G A A C G A G T T C C T T G T C T C a909_a11.seq GTGACATGACTGAAATAGGTAGTTGAGATATCGTATGCAATGTTTGAACA Wajority 1920 1940 1950 GTGACATGACTGAAATAGGTAGTTGAGATATGGTATGCAATGTTTGAACA 2603_ai1.seq GTGACATGACTGAAATAGGTAGTTGAGATATGGTATGCAATGTTTGAACA 18rs21_ai1.seq GTGACATGACTGAAATAGGTAGTTGAGATATGGTATGCAATGTTTGAACA cohl.all.seq 900, GTGACATGACTGAAATAGGTAGTTGAGATATGGTATGCAATGTTTGAACA cjbli1_ai1.seq GTGAGATGACTGAAATAGGTAGTTGAGATATGGTATCCAATGTTTGAACA nem316_ai1.seq GTGACATGACTGAAATAGGTAGTTGAGATATGGTATGCAATGTTTGAACA a909_a11.seq ACCATTTGATAGACCCCCTTCATTATCATTTC Majority 1960 1970 1980 1990 2000 TGTTTAAAATCGAATGTAACCATTTGATAGACCGCCTTCATTATCATTTC 2603_a11.seq 950 TGTTTAAAATCGAATGTAACCATTTGATAGACCGCCTTCATTATCATTTC 18rs21_a11.seq 719 TGTTTAAAATGGAATGTAACCATTTGATAGACCGCCTTCATTATCATTTC 951 TGTTTAAAATCGAATGTAACCATTTGATAGACCGCCTTCATTATCATTTC cjbii1_aii.seq 950 TGTTTAAAATCGAATGTAACCATTTGATAGACCGCCTTCATTATCATTTC nem316_all.seq 951 TGTTTAAAATCGAATGTAACCATTTGATAGACCGCCTTCATTATCATTTC a909_a11.seq TAGAATTTTCTTTAGGTTTGTAAAGACTACAAAATAAATGATGAAAAC Majority 2010 2020. 2030 2040. 2050 TAGAATTTTTCTTTAGGTTTGTAAAGACTACAAAATAAAATGATGAAAC 18rs21. ail. seq TAGAATTTTCTTTAGGTTTGTAAAGACTACAAAATAAAATGATGAAAAC cont.ait.seq TAGAATTTTTCTTTAGGTTTGTAAAGAGTACAAATAAAATAAAATGATGAAGAGBEELAH seq TAGAATTTTTCTTAGGTTTGTAAAGACTACAAATAAAATGATCAAAAC 2000 all seq A A C T A T G T G T G G A T A C A C T A A A A A G A C A C G C T A A T T A G C A A C T C T C T C Majority 2060 2070 2090 2080 2100 AACTATCTTGTGGATACACTAAAAGACACGCTAATTAGCAAACTCTC 2603_a11.seq)50 AACTATCTTGTGGATACACTAAAAAGACACGCTAATTAGCAAACTCTCTC 18rs21_a11.seq 319 AACTATCTTGTGGATACACTAAAAAGACACGCTAATTAGCAAACTCT,CTC cohlaii.seq 151 AACTATCTTGTGGATACACTAAAAAGACACCCTAATTAGCAAACTCTCTC cjbill_ail.seq 150 A A C T A T C T T C T G G A T A C A C T A A A A A G A C A C G C T A A T T A G C A A C T C T C T C nem316 ail. seq 351 A A C T A T C T T G T G G A T A C A C T A A A A A G A C A C G C T A A T T A G C A A A C T C T C T C a909_a11.seq 351

TTCATCATTOTT CIT, CACCIAL TIATTAT ALC LIA OTATTATATGACAAATAAAGC Majority 2110 2120 2130 2140 TTCATCATCTCTCACCATTATTATACTACTATTTATATGACAAATAAAGG 2603_ai1.seq 2100 TTCATCATCTCTCACCATTATTATACTACTATTTATATGACAAATAAAGG 18rs21_ai1.seq 1869 TTCATCATCTCTCACCATTATTATACTACTATTTATATGACAAATAAAGG cohi_aii.seq 1015 TTCATCATCTCTCACCATTATTATACTACTATTTATATGACAAATAÁAGC cjb111_ai1.seq 2100 TTCATCATCTCTCACCATTATTATACTACTATTTATATGACAAATAAAGC nem316_aii.seq 1015 TTCATCATCTCTCTCACCATTATTATACTACTATTTATATGACAAATAAAGC a909_aii.seq. TGATTTTGTTAAAAATATAACTTTGAAAATCCACATATATTTTAATCTT Majority 2160 2170 2180 2190 2200 TGATTTTGTTAAAA TATAACTTTGAAAATCCACATATATTTTTAATCTT 2603_ail.seq 2150 1919 TGATTTGTTAAAA TATAACTTTGAAAATCCACATATATTTTTAATCTT 18rs21_ai1.seq THATTTTGTTAAAA TATAACTTTGAAAATCCACATATATTTTTAATCTT coh1_ail.seq 2151 TGATTTTGTTAAAAATATAACTTTGAAAATCCACATATATTTTTAATCTT cjb111_ai1.seq 2150 TGATTTTGTTAAAAATATAACTTTGAAAATCCACATATATTTTTAATCTT nem316_a11.seq TGATTTTGTTAAAAATATAACTTTGAAAATCCACATATATTTTTAATCTT.a909_ai1.seq CCGTCTGAAAAA.-TAAATAAAATAGTAAAATAAACACGAATTTAAAA Majority 2210 2220 2230 CCGTCTGAAAAA - TAAATAAAATAGTAAAATAAACACGAATTTAAAA 2603_ai1.seq 2199 1968 200 CCGTCTGAAAAAA-TAAATAAAAAATAGTAAAAATAAACACGAATTTAAAA cohl_aii.seq CCGTCTGAAAAA - TAAATAAAAATAGTAAAAATAAA CACGAATTTAAAA cjbiii_aii.seq 201 TAAGCAAATTTTTAAGAAATCTGTGCTAAACTTTAATAGTTTTGTGCT Majority 2260 2270 2280 TAACCAAATTTTTAAGAAATCTGTGCTAAACTTTAATAGTTTTGTCCT 2603_a11.seq TAAGCAAATTTTTAAGAAAATCTGTGCTAAACTTTAAATTGTGCC 18rs21_aif.seq 2017 TAAGCAAATTTTTAAGAAATCTGTGCTAAACTTTAATAGTTTTGTGCT cohl_a11.seq TAAGCAAATTTTTAAGAAAATCTGTGCTAAACTTTAATAGTTTTGTGCT a909_ail.seq 2310 2320 2330 2340 TAATAATAATCAGCACTTACAAAGAACAAAGGAAAGCAAAGCAAGAAGAAC 2603_ai1.seq 298 TAATAATAATCAGCACTTACAAAGAACAAAGGAAAGCGAAAAGCGAAGAAC 18rs21_ai1.seq TAATAATCAGCACTTACAAAGAACAAAGGAAAAGCGAAGAGCGAGAAC cohi_aii.seq TAATAATAATCAGCACTTACAAAGAACAAAGGGAAAAGCGAAGAGAAAAGCGAGAAC cjbiii_aii.seq TTTTAATGAAATTATCGAAGAAGTTATTGTTTTCGGCTGCTGTTTTAACA Majority 2360 -2370 . 2380 2390 TTTTAATGAAATTATCGAAGAAGTTATTGTTTTCGGCTGCTGTTTTAACA 2603_ai1.seq TTTTAATGAAATTATCCAACAAGTTATTCTTTTCCCCTCTCTTTTAACA 18rs21_a11.seq TTTTAATCAATTATCCAACATTATTCTTTTCCCCTCTCTTTTAACA chibit att seq 351 TITIAAT GAAATTAT GCAAGTTATT GTTTT CCCCTCTTTTAACA a909 a11 seq 350 ATG GT G G C G G G T C A A C T G T T G A A C C A G T A G C T C A G T T T G C G A C T G G A A T Majority 2410 2420 2430 2440 2450 398 ATGCTGGCGGGGTCAACTGTTGAACCAGTAGCTCAGTTTGCGACTCGAAT 2603_ail.seq 167 ATG GT G G C G G G T C A A C T G T T G A A C C A G T A G C T C A G T T T G C G A C T G G A A T 18rs21_a11 .seq 399 ATG GTGGCGGGTCAACTGTTGAACCAGTTTGCCAGTTTGCCAATCOALail.seq 399 ATM CT C C C C C C C T C A A C T C T T C A A C C A C T A C C T C A C T T T G C G A C T C G A A T ejbli1_arl .seq ATG CT C C C C C C C T C A A C T G T T G A A C C A C T A C C T C A G T T T C C G A C T G C A A T, nem316_a11.seq 401 ATA CT G C C G G C T C A A C T G T T G A A C C A C T A G C T C A C T T T G C G A C T G G A A T a909_a11.seq. 400

Alignment Report of AI-1_WO_2006/078318 Thursday, July 29, 2004 5:46 PM A C'A COT 6. CAPO A BACA A CAA GAA C C C C A C C A A A A C A A Majority GAGTATT G'T.A 2460 2480 2490 GAGTATTGTAAGAGCTGCAGAAGTGTCACAAGAACGCCCAAGCGAAAACAA 2603_ai1.seq 2448 GAGTATTGTAAGAGCTGCAGAAGTGTCACAAGAACGCCCAGCGAAAACAA 18rs21_ai1.seq 2217 GAGTATTGTAAGAGCTGCAGAAGTGTCACAAGAACGCCCAGCGAAAACAA cohlail.seq 2449 GAGTATTGTAAGAGCTGCAGAAGTGTCACAAGAACGCCCAGCGAAAACAA cjb111_ai1.seq 2449 GACTATTGTAAGAGCTCCAGAAGTGTCACAAGAACGCCCAGCGAAAACAA nem316_ail.seq 2451 2450 GAGTATTGTAAGAGCTGCAGAAGTGTCACAAGAACGCCCAGCGAAAACAA a909_ail.seq CAGTAAATATCTATAAATTACAAGCTGATAGTTATAAATCGGAAATTACT Majority 2510 2520 2530 2540 2550 CAGTAAATATCTATAAATTACAAGCTGATAGTTATAAATCGGAAATTACT 2603_ai1.seq 2498 C.A.G.T.A.A.A.T.A.T.A.C.A.A.G.C.T.G.A.T.A.G.T.T.A.T.A.A.A.T.C.G.G.A.A.T.T.A.C.T. 18rs21_a11.seq 267 CAGTAAATATCTATAAATTACAAGCTGATAGTTATAAATCGGAAATTACT cohl_ail.seq CAGTAAATATCTATAAATTACAAGCTGATAGTTATAAATCGGAAATTACT cjbiii_ai1.seq 1499 CAGTAAATATCTATAAATTACAAGCTGATAGTTATAAATCGGAAATTACT nem316_a11.seq CAGTAAATATCTATAAATTACAAGCTGATAGTTATAAATCGGAAATTACT a909_ail.seq TCTAATGGTGGTATCGAGAATAAAGACGGCGAAGTAATATCTAACTATGC Majority 2560 . 2570 2580 2590 TCTAATGGTGTATCGAGAATAAAGACGGCGAAGTAATATCTAACTATGC 2603_all.seq :548 TCTAATGGTGGTATCGAGAATAAAGACGGCGAAGTAATATCTAACTATGC 18rs21_a11.seq T.CTAATGGTGGTATCGAGAATAAAGACGGCGAAGTAATATCTAACTATGC cohl_ail.seq T C T A A T G G T G G T A T C G A G A A T A A A G A C G G C G A A G T A A T A T C T A A C T A T G C cjbili_aii.seq T C T A A T G G T G G T A T C G A G A A T A A A G A C G G C G A A G T A A T A T C T A A C T A T G C nem316_a11.seq TCTAATGGTGGTATCGAGAATAAAGACGGCGAAGTAATATCTAACTATGC a909_a11.seq T A A A C T T G G T G A C A A T G T A A A A G G T T T G C A A G G T G T A C A G T T T A A A C G T T Majority 2620. 2630 2640 2650 TAAACTTGGTGACAATGTAAAAGGTTTGCAAGGTGTACAGTTTAAAACGTT 2603_ail.seq TAAACTTGGTGACAATGTAAAAGGTTTGCAAGGTGTACAGTTTAAACGTT. 18rs21_ai1_seq TAAACTTGGTGACAATGTAAAAGGTTTGCAAGGTGTACAGTTTAAACGTT cohl_ail.seq TAAACTTGGTGACAATGTAAAAGGTTTGCAAGGTGTACAGTTTAAACGTT cjbiii_aii.seq TAAACTTGGTGACAATGTAAAAGGTTTGCAAGGTGTACAGTTTAAACGTT nem316_ai1.seq TAAACTTGGTGACAATGTAAAAGGTTTGCAAGGTGTACAGTTTAAACGTT a909_aii.seq AGTCAAGACGGATATTTCTGTTGATGAATTGAAAAATTGACAACA Majority 2660 2680 2690 ATAAAGTCAAGACGGATATTTCTGTTGATGAATTGAAAAATTGACAACA 2603_a11.seq 648 417 ATAAAGTCAAGACGGATATTTCTGTTGATGAATTCAAAAATTGACAACA 18rs21_ai1.seq ATAAAGTCAAGACGGATATTTCTGTTGATGAATTGAAAAAATTGACAACA cohl_ail.seq 649 549 ATAAAGTCAAGACGGATATTTCTGTTGATGAATTGAAAAATTGACAACA cjbii1_ai1.seq ATAAAGTCAAGACGGATATTTCTGTTGATGAATTGAAAAATTGACAACA nem316_ai1.seq ATAAAGTCAAGACGGATATTTCTGTTGATGAATTGAAAAAATTGACAACA a909_aii.seq GTTGAAGCAGCACATCCAAAGTTGGAACGATTCTTGAAGGTGTCAG Majority 2710 2720 2730 2740 2750 GTTGAAGCAGCAGATGCAAAAGTTGGAACGATTCTTGAAGAAGGTCTCAC 2603_a11.seq. GTTGAAGCAGCAGATGCAAAAGTTCGAACCATTCTTGAAGGTGTCAG 18rs21_ai1.seq GTTGAAGCAGCAGAAAAGTTGGAACGATTCTTCAAGAAGGTGACATISeq GTTGAAGCAGCAGCATCCAAAACTTGGAACCATTCTTGAAGGTGTCAC cjbill all seq GTTGAAGCAGCAGATCCAAAAGTTGGAACGATTGTTGAAGAACGTGTCAG nem316.ail.seq GTTGAAGCAGGATGCAAAAGTTCGAACCATTCTTGAAGAAGCTCTCAG asos ail seq TCTACCTCAAAAACTAATGCTCAAGCTTTGGTCGTCGATCCTCTGGATT Majority 2760 2770 2780 2790 2800 TCTACCTCAAAAACTAATGCTCAAGGTTTGGTCGTCGATGCTCTCGATT 2603_a11.seq TCTACCTCAAAAACTAATGCTCAAGGTTTGGTCGTCGATGCTCTGGATT 18rs21_a11.seq TCTACCTCAAAAAACTAATGCTCAAGGTTTGGTCGTCGATGCTCTGGATT conl_ai1.seq 49 TCTACCTCAAAAAACTAATGCTCAAGGTTTGGTCGTCGATGCTCTGGATT cjb111_ai1.seq TCTACCTCAAAAAACTAATGCTCAAGGTTTCGTCGTCGATGCTCTGGATT nem316_ail.seq

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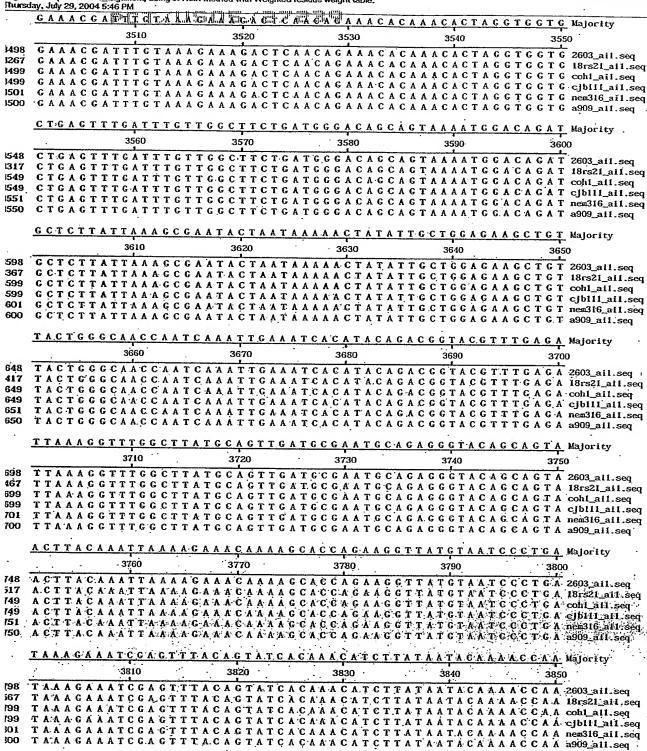
Thursday, July 29, 2004 5:46 PM							
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2798		•		2850			
2567		I A C T T G T A T G T	AGAAGATTTAAAGA	ATTCACCT 2603_all.seq			
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2799	CAAAAGTAATGTGAGAT		AGAAGATTTAAAGA	ATTCACCT cohi_all.seq			
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	2860	2870	2880 2890	•			
20.40		•		2900			
2848 2617	TCAAACATTACCAAAGCT	TATECTETAC	CGTTTGTGTTGGAA	TTACCAGT 2603_ail.seg			
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		•					
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2898							
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949	A A A A C G T T G T A A C T G A T G	AACCAAAAAC	A G A T A A A C A T C T T A	A A A A A T T A cibitt out coo			
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	CCTCACCATCCACCT	T 1 T 1 C C 1 T T C		<u>-</u>			
	G G T C A G G A C G A T G C A G G T	TATACGATIG	GIGAAGAATTCAAA	TGGTTCTT Majority			
	3010	3020	3030 3040	3050			
998	G G T C A G G A C G A T G C A G G T	TATACGATTC	GTGAAGAATTCAAA	T G G T T C T T 2603 all seg			
767	GGTCAGGACGATGCAGGT	TATACGATTG	GTGAAGAATTCAAA	T C C T T C T T 18re21 all see			
999	GGTCAGGACGATGCAGGT	TATACGATTG	G T G A A G A A T T C A A A	TCCTTCTT cobl att con			
999	GGTCAGGACGATGCAGGT	TATACGATTG	CTCAACAATTCAAA	TOOTTOTT SHILL SHEET			
001	G G T C A G G A C G A T G C A G G T	TATACGATTG	G T G A. A. G A A T T C A A. A	TGGTTCTT nem316_ail.seq			
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	G A A A T C T A C A A T C C C T G C	CAATTTACCT	C A C T A T C A A A A A T T	TCAAATTA Malastan			
				•			
	3060	3070	3080 3090	3100			
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KT.	GAAATUTACAATCCCCTGC	CAATTTAGGT	GACTATCAAAAATT	T C'A A A T T A 10 20 21 411 000			
949	GAAATCTACAATCCCTGC	CAATTTAGGT	GACTATGAAAAATT	TGAAATTA cohlail seq			
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• ; •	C T G A T A A A T T T C C A C A T G	G.C.T.T.G.A.C.T.T.A.	TAAATCTCTTCCAA	A A A T C A A C Waterstein			

	3110	3120	3130 3140	3150			
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)99 <u>.</u>	CIGATAAATTTGCAGATG	GCTTGACTTA.	TAAATCTCTTCCAA	AAATCAAC cobt ail con			
)99 101	CIGATAAATTTGCAGATG	GCTTGACTTA	TAAATCTCTTCCAA	AAATCAAC cibiii all con			
101	CTGATAAATTTGCAGATG	CCTTCACTTA	TAAATCTGTTGGAA	A A A T C A A G nem316_ai1.seq			
.00	CTG ATAAATTTG CAGAT-G	GOTTORCLIV	IAAAICTGTTGGAA	AAATCAAG a909_a11.seq			
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ATTGGTTGG AAACACT CAATTAGATCATC ACACTATTGATGAACC Majority 3160 3180 3190 ATTGGTTCGAAAACACTGAATAGAGATGAGCACTACACTATTGATGAACC 2603_ai1.seq 148 ATTGGTTCGAAAACACTGAATAGAGATGAGCACTACTATTGATGAACC 18rs21_ai1.seq 917 149 A T T G G T T C G A A A C A C T G A A T A G A G A T G A G C A C T A C A C T A T T G A T G A A C C cohi_ai1.seq ATTGGTTCGAAAACACTGAATAGAGATGAGCACTACAGTATTGATGAACC cjb111_ai1.seq 149 ATTGGTTCGAAAACACTGAATAGAGATGAGCACTACACTATTGATGAACC nem316_ai1.seq ATTGGTTCGAAAACACTGAATAGAGATGAGCACTACTACTACTATTGATGAACC a909_ail.seq AACAGTTGATAACCAAAATACATTAAAATTACGTTTAAACCAGAGAAT Majority 3210 3220 3230 3240 3250 AACAGTTGATAACCAAAATACATTAAAATTACGTTTAAACCAGAGAAT 2603_ai1.seq 198 AACAGTTGAT,AACCAAAATACATTAAAATTACGTTTAAACCAGAGAAAT 18rs21_a11.seq 967 AACAGTTGATAACCAAAATACATTAAAAATTACGTTTAAACCAGAGAAAT cohl_all.seq AACAGTTGATAACCAAAATACATTAAAATTACGTTTAAACCAGAGAAAT cjbiii_ai1.seq AACAGTTGATAACCAAAATACATTAAAAATTACGTTTAAACCAGAGAAAT nem316_a11.seq 201 AACAGTTGATAACCAAAATACATTAAAATTACGTTTAAACCAGAGAAAT a909_ai1.seq TTAAAGAAATTGCTGAGCTACTTAAAGGAATGACCCTTGTTAAAAATCAA Majority 3260 3270 3280 3290 3300 248 TTAAAGAAATTGCTGAGCTACTTAAAGGAATGACCCTTGTTAAAAATCAA 2603_ai1.seq TTAAAGAAATTGCTGAGCTACTTAAAGGAATGACCCTTGTTAAAAATCAA 18rs21_a11.seq 317 TTAAAGAAATTGCTGAGCTACTTAAAGGAATGACCCTTGTTAAAAATCAA cohlaii.seq 249 TTAAAGAAATTGCTGAGCTACTTAAAGGAATGACCCTTGTTAAAAATCAA cjbiii_aii.seq 249 TTAAAGAAATTGCTGAGCTACTTAAAGGAATGACCCTTGTTAAAAATCAA nem316_ai1.seq TTAAAGAAATTGCTGAGCTACTTAAAGGAATGACCCTTGTTAAAAAATCAA a909_ail.seq GATGCTCTTGATAAAGCTACTGCAAATACAGATGCGGCATTTTTGGA Majority 3320 3330 3340 3350 GATGCTCTTGATAAAGCTACTGCAAATACAGATGCGGCATTTTTTGGA 2603_ail.seq 298 GATGCTCTTGATAAAGCTACTGCAAATACAGATGCGGCATTTTTGGA 18rs21_ai1.seq **367** GATGCTCTTGATAAAGCTACTGCAAATACAGATGCCGGCATTTTTCGA cohl_ail.seq 199 GATGCTCTTGATAAACCTACTGCAAATACAGATGATGCGGCATTTTTGGA.cjb111_ai1.seq 199 GATGCTCTTGATAAAGCTACTGCAAATACAGATGATGCGGCATTTTTCGA nem316_ail.seq 1OI GAT G C T C T T G A T A A A G C T A C T G C A A A T A C A G A T G C G G C A T T T T T G G A a909_ail.seq ATTCCAGTTGCATCAACTATTAATCAAAAGCAGTTTTAGGAAAAGCAA Majority 3360 3370 3380 3390 3400 AATTCCACTTGCATCAACTATTAATGAAAAGCAGTTTTAGGAAAAGCAA 2603_ail.seq AATTCCAGTTGCATCAACTATTAATGAAAAGCAGTTTTAGGAAAAGCAA 18rs21_ai1.seq AATTCCAGTTGCATCAACTATTAATGAAAGCAGTTTTAGGAAAACCAA coh1_ai1.seq AATTCCAGTTGCATCAACTATTAATGAAAAGCAGTTTTAGGAAAAGCAA cjb111_a11.seq AATTCCAGTTGCATCAACTATTAATGAAAAGCAGTTTTAGGAAAAGCAA nem316_ail.seq AATTCCAGTTGCATCAACTATTAATGAAAAGCAGTTTTAGGAAAAGCAA a909_ai1.seq TTGAAAATACTTTTGAACTTCAATATGACCATACTCCTGATAAAGCTGAC Majority 3410 3420 3430 . . 3440 TTGAAAAAACTTTGAACTTCAATATGACCATACTCCTGATAAACCTGAC 2603_ail.seq 98 TTGAAAATACTTTTGAACTTCAATATGACCATACTCCTGATAAAGCTGAC :18rs21 a11.seq TTGAAAATACTTTTGAACTTCAATATGACCATACTCCTGATAAAGCTGAC cibiii alliseq TTGAAAATACTTTGAACTTCAATATGACCTCCTGATAAACCTCAC needicalk seq TTGAAAATACTTTTGAACTTCAATATCACTCCTGATAAACCTGAC 3909 all seq AATCCAAAACCATCTAATCCTCCAAGAAACTTCATACTCCTCC 3460 . 3470 3480 3490 3500 AATCCAAAACCATCTAATCCTCCAAGAAACCAGAAGTTCATACTGCTGC 2603_ail.seq AATCCAAAACCATCTAATCCTCCAAGAAACCAGAAGTTCATAGTGGTGG 18rs21_all.seq AATCCAAAACCATCTAATCCTCCAAGAAACCAGAAGTTCATACTGGTGG cohlail.seq AATCCAAAACCATCTAATCCTCCAAGAAACCAGAAGTTCATACTGGTGG cjb111_ai1.seq 51 AATCCAAAACCATCTAATCCTCCAAGAAACCAGAAGTTCATACTGGTGG nem316_ai1.seq

AATCCAAAACCATCTAATCCTCCAAGAAACCAGAAGTTCATACTGGTGG a909_aii.seq



. Page 12

	CTGAC	A TOAC GTTGA	LACIT'S CT'S	TECHA	·	•
		3860	•		ATACAATTAAA	A A C Majority
3848	CTGAC		3870	3880	3890	3900
3617	CTGAC	A T C A C G G T T G A	TAGTGCTGA	T G C A A C A C C T G	ATACAATTAAA	A A C 2603 ail seg
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3849 3851	CIGACI	ATCACCCTTCL	~		ALAUAALIAAA	A A C cobl att ass
3850	CTGACA	LICACGGTTGA	TAGTGCTGA	T G C A A C A C C T G T G C A A C A C C T G T G C A A C A C C T C	ATACAATTAAA	A.A.C. cjblil_ail.seq
					ALACARITAAA	AAC a909 all sea
:	AACAAA	CCTCCTTCAA	T C C C T A A T A	CTCCTCCTATT		
		3910	3920	3930		C T T Majority
3898	AACAAA	CGTCCTTCAA	r c c c m t t m i		3940	3950
3667	AACAAA	CGTCCTTCAA	CCCTAATA	C T G G T G G T A T T C T G G T G G T A T T T	GGTACGGCTAT	C T T 2603_all.seq
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	1 G 1 C G C	TATCGGTGCT	CGGTGATGO	CTTTTGCTGT	FAAGGGGATCA	A.C.C. Volume
			. 3970	3980	2000	
3948	TGTCGC	TATCGGTGCTC	CCGTGATC			4000
3717 3949	TGTCGC	TATCGGTGCTC	CCGTGATG	CTTTTGCTGT CTTTTGCTGT CTTTTCCTCT	I A A G G G G A T G A	A G C 2603_ail.seq
1949 1949	TOTOGO	TATCGGTGCTG	CGGTGATGG	CTTTTGCTGT7 CTTTTGCTGT7	AAGGGGATGA	A G C 18rs21_ai1.seq
3951	TGTCGC	TATCCCTCCTC	CCCMAL	2 GO 1.4 X 1	LARGEGE AT GA	AGC cibiti ail con
1950	TGTCGC	TATCGGTGCTG	CGGTGATGG	СТТТТ G C T G T 7 СТТТТ G C T G T 7 СТТТТ G C T G T 7	AAGGGGATGA	A G C nem316_ail.seq
		•	· -		AAGGGGATGAA	AGC a909 ail con
• •	G.I C G I A	CAAAAGATAAC	TAAATAAAA	GGCTACTTCTT	AAGTAACCATC	TT Wateries
		. 4010	4020		40.40	. •
1998	G T C G T A	CAAAAGATAAC	TAAATAAAA	GGCTACTTCTT		4050
1767 1999	GTCCTA	CAAAAGATAAC	TAAATAAAA	G G C T A C T T C T T G G C T A C T T C T T	AAGTAACCATO	TT 2603_aii.seq
1999	GIUGTA	CAARACATAAC	T 4 4 4 T 4 4 4 4		A A G L A A C C A T G	TT cohi ait com
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1000	GTCGTA	CAAAAGATAAC	TAAATAAAA	G G C T A C T T C T T G G C T A C T T C T T	AAGTAACCATG	TT nem316_ail.seq
	TAAGAAA	AAGAGAAATAG			H W T A A C C A I G	1 1 a909_a11.seq
		4060	CCITATTTC	TCTTTTTGTCG	TTTTAAAATA	A A Majority
		2000	4070	4080	1000	•
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	•		•		LILLAAAATA	A A agno att coc
	GGAACAT	CATGAAACAA	CATTAAAA	CTTATGTTTTC		
	•	4110	4120	ALCO TO THE TOTAL TO		T C Majority
098	G GVA À C·A T			4130	4140	4150
867	G G A A C A.T	CATGAAACAA	Y CATTAAAAA UCATTAAAAA	TTATGTTTTC	TTTCTCTCA	T G 2603_ail.seg
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099 4	· GAACAT	CATCATACAT	C t m m . t to a .		LITTUTETTEA	T.G cohlatten
100	GAACAT	CATCAAACAAA	CATTAAAA	TTATETTTE	TTTGTGTTGA	T.C. CJD141_a11.seq.
				Sign and the state of the state	I I I I G T T G A	T G 3909 at 1 con
<u>.1</u>	T.A.G.G.G.A	CTATGTTTGGA	ATTACCCAA	ACTETTTE		
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917 7	TAGGGA	CTATGTTTGGA	A T T A C C C A A	ACTGTTTTAGG	GCAAGAACT	C A 2603_ail.seq
149 . 1	TAGGGA	CTATCTTTCA	4 T M		· · · · A A · · · A A C · T · (C.A. 18rs21 at 1 con
149 - 1	TAGGGA	CTATCTTTCAL	4 T T	THE TAR GO	GUAAGAAACT	C A coblest con
150 T	TAGGGA	CTATCTTTCCA	ATTAGCCAA	ACTGTTTTAGC ACTGTTTTAGC	GCAAGAAACT	C A nem316 att sec
	"	n · o · i · i · o · o · A	A I I A G C C A A	A C T G T T T T A G C A C T G T T T T A G C	G C A A G A A A C T (C A a909_ail.seq

Alignment Report of Al-1 \underline{WO} 2006/078318 method with Weighted residue weight table CT/US2005/027239 Thursday, July 29, 2004 5:46 PM ATT CHE CATC TIC A A C CAA G G G A T A T T G A T C G T C C A A A T C Majority TCAGTTGACC 4210 4230 4240 4250 TCAGTTGACGATTGTTCATCTTGAAGCAAGGGATATTGATCGTCCAAATC 2603_ai1.seq TCAGTTGACGATTGTTCATCTTGAAGCAAGGGATATTGATCGTCCAAATC 18rs21_ai1.seq TCAGTTGACGATTGTTCATCTTGAAGCAAGGGATATTGATCGTCCAAATC cohl_ai1.seq TCAGTTGACGATTGTTCATCTTGAAGCAAGGGATATTGATCGTCCAAATC cjbill_ail.seq 4199 TCAGTTGACGATTGTTCATCTTGAAGCAAGGGATATTGATCGTCCAAATC nem316_ai1.seq 4201 TCAGTTGACGATTGTTCATCTTGAAGCAAGGGATATTGATCGTCCAAATC a909_ai1.seq 4200 CACAGTTGGAGATTGCCCCTAAAGAAGGACTCCAATTGAAGGAGTACTC Majority 4260 4270 4280 4290 4300 CACAGTTGGAGATTGCCCCTAAAGAAGGGACTCCAATTGAAGGAGTACTC 2603_al1.seq 4248 CACAGTTGGAGATTGCCCCCTAAAGGAAGGGACTCCAATTGAAGGAGTACTC 18rs21_a11.seq 4017 CACAGTTGGAGATTGCCCCTAAAGAAGGGACTCCAATTGAAGGAGTACTC cohi_all.seq CACAGTTGGAGATTGCCCCTAAAGAAGGGACTCCAATTGAAGGAGTACTC cjblli_all.seq 4249 1249 CACAGTTGGAGATTGCCCCTAAAGGAAGGGACTCCAATTGAAGGAGTACTC nem316_a11.seq (251 CACAGTTGGAGATTGCCCCTAAAGAAGGGACTCCAATTGAAGGAGTACTC a909_ail.seg 1250 TATCAGTTGTACCAATTAAAATCAACTGAAGATGGCGATTTGTTGGCACA Majority 4310 4320 4330 4340 4350 TATCAGTTGTACCAATTAAAATCAACTGAAGATGGCGATTTGTTGGCACA 2603_ai1.seq 1298 TATCACTTGTACCAATTAAAATCAACTGAAGATGGCGATTTGTTGGCACA 18rs21_ai1.seq 1067 TATCAGTTGTACCAATTAAAATCAACTGAAGATGGCGATTTGTTGGCACACohl_ai1.seq 1299 TATCAGTTGTACCAATTAAAATCAACTGAAGATGGCGATTTGTTGGCACA cjbiii_aii.seq 1299 TATCAGTTGTACCAATTAAAATCAACTGAAGATGGCGATTTGTTGGCACA nem316_all.seq 1301 TATCACTTCTACCAATTAAAATCAACTCAAGATGGCGATTTCTTGGCACA a909_ai1.seq 1300 TTGGAATTCCCTAACTATCACAGAATTGAAAAAACAGGCGCAGCAGTTT Majority 4360 4370 4380 4390 4400 TTGGAATTCCCTAACTATCACAGAATTGAAAAAACAGGCGCAGGTTT 2603_a11.seq 1348 TTGGAATTCCCTAACTATCACAGAATTGAAAAACAGGCGCAGCAGGTTT 18rs21_aii.seq 1117 TTGGAATTCCCTAACTATCACAGAATTGAAAAAACAGGCGCAGGTTT cohl_ail.seq 1349 TTGGAATTCCCTAACTATCACAGAATTGAAAAAACAGGCGCAGCAGGTTT cjb111_a11.seq 1349 TTGGAATTCCCTAACTATCACAGAATTGAAAAAACAGGCGCAGCAGGTTT nem316_ail.seq 1351 TTGGAATTCCCTAACTATCACAGAATTGAAAAAACAGCCGCACCAGGTTT a909_ai1.seq 1350 TTGAAGCCACTACTAATCAACAAGGAAAGCTACATTTAACCAACTACCA Majority 4410 4420 4430 4440 4450 TTGAAGCCACTACTAATCAACAAGGAAAGGCTACATTTAACCAACTACCA 2603_ail.seq 398 TTGAAGCCACTACTAATCAACAAGGAAAGGCTACATTTAACCAACTACCA 18rs21_a11.seq 167 TTGAAGCCACTACTAATCAACAAGGCTACATTTAACCAACTACCA cohlail.seq 399 TTGAAGCCACTACTAATCAACAAGGAAAGGCTACATTTAACCAACTACCA cjbli1_ail.seq 399 TTGAAGCCACTACTAATCAACAAGGAAAGGCTACATTTAACCAACTACCA nem316_ai1.seq 401 TTGAAGCCACTACTAATCAACAAGGCTACATTTAACCAACTÁCCA a909-a11.seq 400 CATGGAATTTATTATCGTCTGGCGGTTAAAGCCGGTGAAAAAATCGTAA Majority 4460 4470 4480 4490 4500 GATGGAATTTATTATCGTCTGGCGGTTAAAGCCGGTGAAAAAAATCGTAA 2603 ail seq 448 GATGGAATTTATTATGGTCTGGCGTTAAAGCCGGTGAAAAAATCGTAA 186821 all seq 217 GATGGAATTTATTATCGTCTGGCCCTTAAAGCCGGTGAAAAAATCGTAACcohlat1.seq 449 GATGGAATTTATTATGCTGTGGCCGTTAAACCCCCGTGVAAAAACCTCCTAA cibiit ail seg 449 451 TGTGTCAGCTTCTTGGTTGACTTGTCTGAGGATAAAGTGATTATCCTA 4510 4520 4530 . 4540 TGTCTCAGCTTTCTTGGTTGACTTGTCTGAGGATAAAGTGATTTATCCTA.2603_aif.seq 498 TGTCTCAGCTTTCTTGGTTGACTTGTCTGAGGATAAAGTGATTTATCCTA. 18rs21_ail_seq TGTCTCAGCTTTCTTGGTTGACTTGTCTGAGGATAAAGTGATTTATCCTA cohl_all.seq TGTCTCAGCTTTCTTGGTTGACTTGTCTGAGGATAAAGTGATTTATCCTA cjbiii_ai1.seq TGT-CTCAGCTTTCTTGGTTGACTTGTCTGAGGATAAAGTGATTTATCCTA nem316_a11.seq 501

TGTCTCAGCTTCTTGGTTGACTTGTCTGAGGATAAAGTGATTTATCCTA a909_ail.seq

Alignment Report of At-1_WO 2006/078318

Alignment Report of At-1_word and the country of the co Thursday, July 29, 2004 5:46 PM CTCCACCACCACACTTTCCACTTCCTTAAAGTTCCTCGAT Majority AAATCATCE 4560 4580 4590 4600 AAATCATCTGGTCCACAGGTGAGTTGGACTTGCTTAAAGTTGGTGTGGAT 2603_ail.seq 4548 AAATCATCTGGTCCACAGGTGAGTTGGACTTGCTTAAAGTTGGTGTGGAT 18rs21_ai1.seq 4317 A A A T C A T C T G G T C C A C A G G T G A G T T G G A C T T G C T T A A A G T T G G T G T G G A T cohl_ail.seq 1549 AAATCATCTGGTCCACAGGTGAGTTGGACTTGCTTAAAGTTGGTGTGGAT cjbiii_ai1.seq 4549 AAATCATCTGGTCCACAGGTGAGTTGGACTTGCTTAAAGTTGGTGTGGAT nem316_ail.seq 4551 1550 A A A T C A T C T G G T C C A C A G G T G A G T T G G A C T T G C T T A A A G T T G G T G T G C A T a909_ail.seq G G T G A T A C C A A A A A A C C A C T A G C A G C C G T T G T C T T T G A A C T T T A T G A A A A Majority 4610 4620 4630 4640 4650 G G T G A T A C C A A A A A A C C A C T A G C A G G C G T T G T C T T T G A A C T T T A T G A A A A 2603_aii.seq 1598 G G T G A T A C C A A A A A A C C A C T A G C A G C C G T T G T C T T T G A A C T T T A T G A A A 18rs21_ail.seq 1367 G G T G A T A C C A A A A A C C A C T A G C A G C C G T T G T C T T T G A A C T T T A T G A A A A cohi_aii.seq 1599 1599 GGTGATACCAAAAACCACTAGCAGGCGTTGTCTTTGAACTTTATGAAAA cjbiil_aii.seq GGTGATACCAAAAAACCACTAGCAGGCGTTGTCTTTGAACTTTATGAAA nem316_ail.seq 1601 G G T G A T A C C A A A A A A A C T A G C A G G C G T T G T C T T T G A A C T T T A T G A A A A a a 909_ail.seq 1600 GAATGGTAGGACTCCTATTCGTGTGAAAATGGGGTTCCATCTCAAGATA Majority 4660 4680 4690 4700 1648 GAATGGTAGGACTCCTATTCGTGAAAAATGGGGTGCATTCTCAAGATA 2603_a11.seq. GAATGGTAGGACTCCTATTCGTGTGAAAATGGGGTGCATTCTCAAGATA 18rs21_ai1.seq GA-ATGGTAGGACTCCTATTCGTGTGAAAATGGGGTGCATTCTCAAGATA cohl_ail.seq GAATGGTAGGACTCCTATTC.GTGTGAAAATGGGGTGCATTCTCAAGATA cjbiii_aii.seq GAATGGTAGGACTCCTATTCGTGTGAAAATGGGGTGCATTCTCAAGATA nem316_a11.seq 1651 GAATGGTAGGACTCCTATTCGTGAAAAATGGGGTGCATTCTCAAGATA a909_aii.seq 1650 TTGACGCTGCAAAACATTTAGAAACAGATTCATCAGGGCATATCAGAATT Majority 4710 4720 4730 4740 4750 TTGACGCTGCAAAACATTTAGAAACAGTTCATCAGGGCATATCAGAATT 2603_ail.seq 1698 1467 TTGACGCTGCAAAACATTTAGAAACACTTCATCAGGGCATATCAGAATT 18rs21_ai1.seq TTGACGCTGCAAAACATTTAGAAACAGATTCATCAGGGCATATCAGAATT cohl_all.seq TTGACGCTGCAAAACATTTAGAAACAGATTCATCAGGGCATATCAGAATT cjb111_ai1.seq TTGACGCTGCAAAACATTTAGAAACAGATTCATCAGGGCCATATCAGAATT nem316_ail.seq. TTGACCCTGCAAAACATTTAGAAACAGATTCATCAGGGCATATCAGAATT a909_a11.seq TCCGGGCTCATCCATGGGGACTATGTCTTAAAAGAAATCGAGACACAGTC Majority 4760 4780 4770 4790 4800 TCCGGGCTCATCCATGGGGACTATGTCTTAAAAGAAATCGAGACACAGTC 2603_ail.seq 1748 517 TCCGGGCTCATCCATGGGGACTATGTCTTAAAAGAATCGAGACACAGTC 18rs21_xi1.seq TCCGGGCTCATCCATGGGGACTATGTCTTAAAAGAATCGAGACACAGTC cohl_ail.seq 1749 TCCGGGCTCATCCATGGGGACTATGTCTTAAAAGAATCGAGACACAGTC cjb111_ail.seq 1749 TCCGGGCTCATCCATGGGGACTATGTCTTAAAAGAATCGAGACACAGTC nem316_ai1.seq 1751 TCCGGGCTCATCCATGGGGACTATGTCTTAAAAAGAATCGAGACACAGTC a909_aii.seq 1750 A G G A T A T C A G A T C G G A C A G G C A G A G A C T G C T G T G A C T A T T G A A A A T C A A Majority 4810 4830 4840 ..4850 A G.G A T A T C A G A T C G G A C A G G C A G A G A C T G C T G T G A C T A T T G A A A A T C A A 2603 all seq 1798 AGGATATGAGATCGGACAGGCAGAGACTGCTGTGAGTTTGAAAAATCAA 18rs21_ai1.seq A G G A T A T C A G A T C G G A C A G G C A G A G A C T G C T G T G A C T A T T G A A A A T C A A cohl all seq 1799 A G.G A T.A. T.C.A. G.A. G.A.G.A.G.A.G.A.G.A.G.A.G.A.G.T.G.C.T.G.T.T.G.A.A.A.A.T.C.A.A. cjbilizativseq A.G.G. A.T. A.T.C. A.G. A.T. C. G. C. A.G. G. C. A.G. A.G. A. C. T. G. C. T. C. T. T. G. A. A. A. A. T. C. A. A. nem316 att seq. 1801:-AGGATATOAGATEGGACAGGGAAGAGTGTGTGAGTTGAAAAAATCAA agog all seq 1800 AAACACTTCCGACTAACGATTGAAATAAAAAATCCCGACACCTAAAGTC 4870 4860 4880 4890 4900 AAACAGTAACAGTAACGATTGAAAATAAAAAGTTCCGACACCTAAAGTG 2603_ail.seq 1848 AAACAGTAACAGTAACGATTGAAATAAAAATCTTCCGACACCTAAAGTG 18rs21_ai1.seq 617 A A A C A G T A A C A G T A A C G A T T G A A A A T A A A A A G T T C C G A C A C C T A A A G T G continuit. seq R49 849 AAACAGTAACAGTAACGATTGAAAATAAAAAAGTTCCGACACCTAAAGTG cjb111_a11.seq AAACAGTAACAGTAACGATTGAAAATAAAAAGTTCCCACACCTAAAGTG nem316_a11.seq

AAACAGTAACAGTAACGATTGAAAATAAAAGTTCCGACACCTAAAGTG a909_ai1.seq

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WO 2006/078318

Alignment Report of Al-1_alignment, using J. Hein method with Weighted residue weight table. Thursday, July 29, 2004 5:46 P.M. CCATCTEGA GGACTCTT 4910 4920 4930 4940 4950 CCATCTCGAGGAGGTCTTATTCCCAAAACAGGTGAGCAACAGGCAATGGC 2603_ai1.seq 4898 4667 CCATCTCGAGGAGGTCTTATTCCCAAAACAGGTGAGCAACAGGCAATGGC 18rs21_ai1.seq 4899 CCATCTCGAGGAGGTCTTATTCCCAAAACAGGTGAGCAACAGGCAATGGC cohi_ai1.seq CCATCTCGAGGAGCTCTTATTCCCAAAACAGGTGAGCAACAGGCAATGGCCjbli1_ai1.seq 4899 CCATCTCGAGGAGGTCTTATTCCCAAAACAGGTGAGCAACAGGCAATGGC nem316_ail.seq 4901 C C A T C T C G A G G T C T T A T T C C C A A A A C A G G T G A G C A A C A G G C A A T G G C a909_ail.seq A C T T G T A A T T A T T C C T C C T A T T T T A A T T C C T T T A G C C T T A C G A T T A C T A T Majority 4960 4970 4980 4990 5000 ACTT CTAATT ATT CGT CGT ATTTTAATT GCT TTAGCCTTAC GATT ACTAT 2603_ail.seq 4948 ACTT GT AATT ATT G GT G GT ATTTT AATT G CTTT AG C CTT AC G ATT ACT AT 18rs21_ai1.seq 4717 ACTTGTAATTGGTGGTATTTTAATTGCTTTAGCCTTACGATTACTAT cohl_all.seq 4949 4949 ACTTGTAATTATTCGTGGTATTTTAATTCCTTTAGCCTTACGATTACTAT cjb111_ai1.seq ACTT GTAATTATT GGT GGT ATTTTAATT GCTTT AGCCTTAC GATT ACTAT nem316_a11.seq CAAAACATCGGAAACATCAAAATAAGGATTAGCATGGGACAAAAATCAAA Majority 5010 5030 5040 5050 4998 CAAAACATCGGAAACATCAAAATAAGGATTAGCATGGGACAAAAATCAAA 2603_ail.seq 4767 CAAAACATCGGAAACATCAAAATAAGGATTAGCATGGGACAAAAATCAAA 18rs21_a11.seq CAAAACATCGGAAACATCAAAATAAGGATTAGCATGGGACAAAAATCAAA cohl_all.seq 1999 CAAAACATCGGAAACATCAAAATAAGGATTAGCATGGGACAAAAATCAAA cjbiil_ail.seq 5001 CAAAACATCGGAAACATCAAAATAAGGATTAGCATGGGACAAAAATCAAA nem316_a11.seq CAAAACATCGGAAACATCAAAATAAGGATTAGCATGGGACAAAAATCAAA a909_ai1.seq 5000 A A T A T C T C T A G C T A C G A A T A T T C G T A T A T G G A T T T T T C G T T T A A T T T T C T Majority . 5070 5080 5090 5100 5048 AATATCTCTAGCTACGAATATTCGTATATGGATTTTTCGTTAATTTCT 2603_ail.seq AATATCTCTAGCTACGAATATTCGTATATGGATTTTTCGTTTAATTTTCT 18rs21_ail.seq 1817 AATATCTCTAGCTACCAATATTCGTATATGGATTTTTCGTTTAATTTTCT cohl_aii.seq 5049 5049 AATATCTCTAGCTACGAATATTCGTATATGGATTTTTCGTTTAATTTTCT cjbiii_ai1.seq AATATCTCTAGCTACGAATATTCGTATATGGATTTTTCGTTTAATTTCT nem316_a11.seq 5051 **5050** A ATATCTCTAGCTACCAATATTCGTATATGGATTTTTCGTTTAATTTTCT a909_all.seq TAGCGGGTTTCCTTGTTTTGGCATTTCCCATCGTTAGTCAGGTCATGTAC Majority 5110 5120 5130 5140 5150 TAGCGGGTTTCCTTGTTTTGGCATTTCCCATCGTTAGTCAGGTCATGTAC 2603_ai1.seq TAGCGGGTTTCCTTGTTTTGGCATTTCCCATCGTTAGTCAGGTCATGTAC 18rs21_ai1.seq TAGCGGGTTTCCTTGTTTTGGCATTTCCCATCGTTAGTCAGGTCATGTAC cohl_ail.seq TAGCGGGTTTCCTTGTTTTGGCATTTCCCATCGTTAGTCAGGTCATGTAC cjbili_ail.seq TAGCGGGTTTCCTTGTTTTGCCATTTCCCATCGTTAGTCACGTCATGTAC ném316_ail.seq TAGCGGGTTTCCTTGTTTTGGCATTTCCCATCGTTAGTCAGGTCATGTAC a909_ail.seq TTTCAAGCCTCTCACGCCAATATTAATGCTTTTAAGAAGCTGTTACCAA Majority 5160 5170 5180 5190 5200 148 TTTCAAGCCTCTCACCCCAATATTAATGCTTTTAAAGAAGCTGTTACCAA 2603_a11.seq TTTCAAGCCTCTCACGCCAATATTAATGCTTTTAAAGAAGCTGTTACCAA 18rs21 ail seq 917 149 TTTCAAGCCTCTCACCCCAATATTAATCCTTTTAAAGAAGCTCTTACCAA cjbiil aif seq 149 TIT CAAGCCTCTCACGCCAATATTAATGCTTTTAAAGAAGCTCTTTACCAA nee316 all seq 151 GATTGACCCGGGAGATTAATCCCGCGTTTAGACTTCCTTAATCCTTAA 5210 : 5220 5230 5240 GATTGACCGGGTGGAGATTAATCGGCGTTTAGAACTTGCTTATGCTTATA. 2603_all.seq 198 GATTGACCGGGTGGAGATTAATCGGCGTTTAGAACTTGCTTATGCTTATA i8rs21_ai1.seq 967 GATTGACCGGGTGCACATTAATCCCCCTTTAGAACTTGCTTATGCTTATA cohlaii.seq 199 GATTGACCGGGTGGAGATTAATCGGCGTTTAGAACTTGCTTATGCTTATAcjbii1_ai1.seq GATTGACCGGGTGGAGATTAATCGGCCTTTAGAACTTGCTTATTAGAACTTGCTTATAGAACTTGCTTATAGAACTTGCTTATA

GATTGACCGGGTGGAGATTAATCGGCGTTTAGAACTTGCTTATGCTTATA a909_ali_seq

Alignment Report of Al-1_WO_2006/078318 Thursday, July 29, 2004 5:46 PM N. July 29, 2004 5:46 PM ACGCCAGT ATAGCAGGG TOCCCAA A A CTTAA T GGCGAATATCCAGCGCTTAAA Majority 5260 5280 5290 ACCCCAGTATACCAGCTCCAAAACTAATGGCCAATATCCAGCCCTTAAA 2603_all.seq 5248 ACCCCAGTATACCAGGTCCCAAAACTAATGGCGAATATCCAGCCCTTAAA 18rs21_ai1.seq 5017 A C G.C C A G T A T A G C A G G T G C C A A A A C T A A T G G C G A A T A T C C A G C G C T T A A A cohi_aii.seq 5249 ACCCCAGTATACCAGGTCCCAAAACTAATGGCGAATATCCAGCGCTTAAA cjb111_a11.seq 5249 ACGCCAGTATAGCAGGTGCCAAAACTAATGGCGAATATTCAGCGCTTAAA nem316_ai1.seq 5251 ACCCCAGTATACCAGGTCCCAAAACTAATCGCAATATCCACCCCTTAAA a909_ai1.seq 5250 GACCCCTACTCTGCTGAACAAAGCAGGCAGGGTCGTTGAGTACGCCCG Majority 5310 5320 5330 5340 5298 GACCCCTACTCTGCTGAACAAAGCAGGCAGGGTCGTTGAGTACGCCCC 2603_ail.seq GACCCCTACTCTGCTGAACAAAGCAGGGGGTCGTTGAGTACGCCCG 18rs21_a11.seq 5067 GACCCCTACTCTGCTGAACAAAGCAGGGGGGGGGTCGTTGAGTACGCCCG cohl_ail.seq 5299 GACCCCTACTCTGCTGAACAAAGCAGGCAGGGGTCGTTGAGTACGCCCG cjb111_ai1.seq 5299 GACCCCTACTCTGCTGAACAAAGCAGGGGGTCGTTGAGTACGCCCG nem316_a11.seq 5301 GACCCCTACTCTGCTGAACAAAGCAGGCAGGGGTCGTTGAGTACGCCCG a909_ail.seq 5300 CATGCTTGAAGTCAAAGAACAAATAGGTCATGTGATTATTCCAAGAATTA Majority 5360 5380 5390 CATCCTTGAAGTCAAAGAACAAATAGGTCATGTGATTATTCCAAGAATTA 2603_a11.seq 5348 CATGCTTGAAGTCAAAGAACAAATAGGTCATGTGATTATTCCAAGAATTA 18rs21_ai1.seq C'ATGCTTGAAGTCAAAGAACAAATAGGTCATGTGATTATTCCAAGAATTA cohl_ail.seq **i349** CATGCTTGAAGTCAAAGAACAAATAGGTCATGTGATTATTCCAAGAATTA cjbill_ail.seq **i349** CATCCTTCAAGTCAAACAAAATAGGTCATGTGATTATTCCAAGAATTA nen316_ail.seq CATGCTTGAAGTCAAACAAATAGGTCATGTGATTATTCCAAGAATTA a909_ai1.seq ATCAGGATATCCCTATTTACGCTGCCTCTGCTGAAGAAATCTTCAGAGG Majority 5430 5440 5450 ATCAGGATATCCCTATTTACGCTGGCTCTGCTGAAGAATCTTCAGAGC 2603_a11.seq ATCAGGATATCCCTATTTACGCTGGCTGTGAAGAAATCTTCAGAGG 18rs21_ai1.seq ATCAGGATATCCCTATTTACGCTGGCTCTGCTGAAGAAATCTTCAGAGG cohlail.seq ATCAGGATATCCCTATTTACGCTGGCTCTGCTGAAGAAATCTTCAGAGG cjbili_ail.seq ATCAGGATATCCCTATTTACGCTGGCTCTGCTGAAGAAATCTTCAGAGG nem316_ail.seq ATCAGGATATCCCTATTTACGCTGGCTGCTGAAGAAATCTTCAGAGG a909_ail.seq G G C G T T G G A C A T T T A G A G G G G A C C A G T C T T C C A G T C G T G G T G A G T C A A C Majority 5460 5480 5470 5490 GGCGTTGGACATTTAGAGGGGACCAGTCTTCCAGTGGTGGTGAGTCAAC 2603_ail.seq 448 GGCGTTGGACATTTAGAGGGGACCAGTCTTCCAGTCGGTGGTGAGTCAAC 18rs21_ail.seq 217 G G C G T T G G A C A T T T A G A G G G G A C C A G T C T T C C A G T C G G T G G T G A G T C A A C cohl ail.seq 449 449 GGCGTTGGACATTTAGAGGGGGACCAGTCTTCCAGTCGGTGGTGAGTCAAC cjb111_ai1.seq 451 GGCGTTGGACATTTAGAGGGGACCAGTCTTCCAGTCGTGGTGAGTCAAC nem316_aif.seq G G C G.TT G G A C A T T T A G A G G G G A C C A C T C T T C C A G T C G G T G G T G A G T C A A C a909_a11.seq 450 T C A T G C C G T T C T A A C T G C C C A T C G A G G G C T A C C A A C G G C C A A G C T A T T T A Majority 5510 5520 5530 5540 5550 TCATGCCGTTCTAACTGCCGATCGAGGGCTACCAACGCCAAGCTATTTA 2603_ai1.seq T C A T G C C G T T C T A A C T G C C C A T C G A G G G C T A C C A A C C G C C A A G C T A T T T A 18rs21_a11 seq T C A T G C C G T T C T A A C T G C C C A T C G A G G C C T A C C A A C G G C C A A G C T A T T T A contail seq T C A T G C C G T T C T A A C T G C C A T C G A G G G G T A C C A A C G G C C A A G C T A T T T A cibilitatic seq TCATGCCGTTCTAACTGCCCATCGAGGGGTACCAACGGCAAGGCAAGGTTATTA nem316 att seq 50 I TCATGCCGTTCTAACTGCCATCGAGGCTACGAACGCTATTA a009 ail seq 500 CCAATTTAGACAAGGTAACAGTAGGTGACCGTTTTTACATTGAACACATC Majority 5560 5570 5580 · 5590 5600 C,C A A T T T A G A C A A G G T A A C A G T A G G T G A C C G T T T T T A C A T T G A A C A C A T C 2603_a11.seq 548 C.C.A.A.T.T.A.G.A.C.A.G.G.T.A.G.G.T.A.G.G.T.G.A.C.A.T.T.G.A.A.C.A.C.A.T.C. 18rs21_a11.seq C C A A T T T A G A C A A G G T A A C A G T A G G T G A C C G T T T T T A C A T T G A A G A C A.T C coh1_ai1.seq 549 CCAATTTAGACAAGGTAACAGTAGGTGACCGTTTTTACATTGAACACATCcjbiii_ail.seq 549 C C A A T T T A G A C A A G G.T A A C A G T A G G T G A C C G T T T T T A C A T T G A A C A C A T C nea316_ail.seq 551 C C A A T T T A G A C A A G G T A A C A G T A G G T G A C G G T T T T T A C A T T G A A C A C A T C a909_a11.seq

tignment Report of Al-1_tanguneau, usung J: trem method with Weighted residue weight table. hursday, July 29, 2004 5:46 PM GGCGGAAATTTCGCCTTATCACGTACGACGTACAAATCAAAGTTATCGCCCCTGA Majority 5610 5620 5630 5640 G G C G G A A A G A T T G C T T A T C A G G T A G A C C A A A T C A A G T T A T C G C C C C T G A 2603_ail.seq G G C G G A A A G A T T G C T T A T C A G G T A G A C C A A A T C A A G T T A T C G C C C T G A 18rs21_a11.seq G G C G G A A A G A T T G C T T A T.C A G G T A G A C C A A A T C A A A G T T A T C G C C C T G A coh1_ai1.seq GGCGGAAAGATTGCTTATCAGGTAGACCAAATCAAAGTTATCGCCCCTGA cjb111_a11.seq 601 G G C G G A A A G A T T G C T T A T C A G G T A G A C C A A A T C A A G T T A T C G C C C T G A nem316_a11.seq 600 G G C G G A A A G A T T G C T T A T C A G G T A G A C C A A A T C A A A G T T A T C G C C C T C.A a909_al1.seq T C A G T T A G A G G A T T T G T A C G T G A T T C A A G G A G A A G A T C A C G T C A C C C T A T Majority 5660 5670 5680 5690 5700 TCAGTTAGAGGATTTGTACGTGATTCAAGGAGAAGATCACGTCACCCTAT 2603_ai1.seq 648 417 T C A G T T A G A G G A T T T G T A C G T G A T T C A A G G A G A T C A C G T C A C C C T A T 18rs21_ai1.seq T C A G T T A G A G G A T T T G T A C G T G A T T C A A G G A G A A G A T C A C G T C A C C C T A T cohl_all.seq 649 TCAGTTAGAGGATTTGTACCTGATTCAAGGAGATCACGTCACCCTAT cjb111_ai1.seq 649 T C A G T T A G A G G A T T T G T A C G T G A T T C A A G G A G A T C A C G T C A C C C T A T nem316_ai1.seq 651 T C A G T T A G A G G A T T T G T A C G T G A T T C A A G G A G A A G A T C A C G T C A C C C T A T a909_ail.seq 650 TAACTTGCACACCTTATATGATAAATAGTCATCCCTCCTCCTTCGAGGC Majority 5710 5720 5730 5740 5750 698 TAACTTGCACACCTTATATGATAAGTCATCGCCTCCTCGTTCGAGGC. 2603_ail.seq TAACTTGCACACCTTATATCATAAATAGTCATCGCCTCCTCGTTCGAGGC 18rs21_ai1.seq 467 TAACTT G C A C A C C T T A T A T G A T A A A T A G T C A T C G C C T C C T C G T T C G A G G C cohl_ail.seq 599 TAACTTGCACACCTTATATGATAAATAGTCATCGCCTCCTTCGAGGCCjbii1_aii.seq 699 TAACTT GCACACCTTATAT GATAAATAGT CATCCCTCCTCGTTCGAGGC nem316_ail.seq 701 TAACTT G CACACCT TATAT GATAAATAGT CATCGCCT CCTCGTT CGAGGC a909_ail.seq 700 A A G C G A A T T C C T T A T G T G G A A A A A A C A G T G C A G A A G A T T C A A A G A C C T T Majority 5770 5780 5790 5800 748 AAGCGAATTCCTTATGTGGAAAAACAGTGCAGAAAGATTCAAAGACCTT 18rs21_ai1.seq 517 AAGCGAATTCCTTATGTGGAAAAACAGTGCAGAAAGATTCAAAGACCTT cohi_ai1.seq 749 AAGCGAATTCCTTATGTGGAAAAAACAGTGCAGAAAGATTCAAAGACCTT cjb111_at1.seq 749. AAGCGAATTCCTTATGTGGAAAAAACAGTGCAGAAAGATTCAAAGACCTT nem316_ai1.seq 751 A A G C G A A T T C C T T A T G T G G A A A A A A C A G T G C A G A A A G A T T C A A A G A C C T T a909_a11.seq 750 CAGGCAACAACAATACCTAACCTATGCTATGTGGGTAGTCGTTGGACTTA Majority 5820 5830 :5850 5840 CAGGCAACAATACCTAACCTATGCTATGTGGGTAGTCGTTGGACTTA 2603_ail.seq 798 CAGGCAACAACAATACCTAACCTATGCTATGTGGGTAGTCGTTGGACTTA 18rs21_ai1.seq 567 CAGGCAACAACATACCTAACCTATCCTATGTGGGTACTCGTTGGACTTA cohl_ait.seq 799 CAGGCAACAACAATACCTAACCTATGCTATGTGGGTAGTCGTTGGACTTA cjb111_ai1.seq 799 CAGGCAACAACAATACCTAACCTATGCTATGTGGGTAGTCGTTGGACTTA nem316_ai1.seq 301 300 CAGGCAACAACAATACCTAACCTATGCTATGTGGGTAGTCGTTGGACTTA a909_a11.seq TCTTGCTGTCGCTTCTCATTTGGTTTAAAAAGGCGAAACACAGAAAAGCGG 5870 5880 · 5890 . 5900 TCTTGCTGTCGCTTCTCATTTGGTTTAAAAAGACGAAAAAAGCCGG 2603_ai1.seq 317 149 149 TCTTCCTCTCCTCTCTCATTTCCTTTAAAAACCCAAACACCCAAAACCCCCnem316 all seq 151 T C T T G C T G T C G C T T C T C A T T T G G T T T A A A A G A C G A A A C A G A A A A C C G G asob at seq 150 A G A A G A A T G A A A A G C G G C T A G T C A A A A T A G T C A C A A T A A T T C G A A T A MAJORITY 5910 5920 5930 5940 5950 A G A A A G A A T G A A A A G C G G C T A G T C A A A A T A G T C A C A A T A A T T C G A A A T A 2603_ai1.seq AGAAAGAATGAAAAGCCGCTAGTCAAAATAGTCACAATAATTCGAAATA iBrs21_ai1.seq 67 A G A A A G A A T G A A A A G G G G C T A G T C A A A A T A G T C A C A A T A A T T C G A A A T A coh1_a11.seq 199 399 AGAAAGAATGAAAAGCCGGCTAGTCAAAATAGTCACAAAATAGTCGAAATAcjb111_ai1.seq AGAAAGAATGAAAAAGCCGGCTAGTCAAAATAGTCACAAATACTCGAAATA nem316_a11.seq Ю1

AGAAAGAATGAAAAGCCGGCTAGTCAAAATAGTCACAATAATTCGAAAATAa909_a11.seq

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5949	ATAAAATCAGAACCCTC		GTCTGATTCTCTTATTT cohl_ail.seq
5951	ATAAAATCAGAACCCTC	CATTTTTCTCATCCCAA	GTCTGATTCTCTTATTT contail.seq GTCTGATTCTCTTATTT cjb111_ail.seq GTCTGATTCTCTTATTT nem316_ail.seq
5950	ATAAAATCAGAACCCTC	CATTTTTCTCATCCCAL	GTCTGATTCTCTTATTT nem316_ail.seq GTCTGATTCTCTTATTT a909_ail.seq
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5817	TCAATTTAAGCGGGAAG	TCGCTAACATTCATAC	TAATACGGTTGAACGAC 2603_a11.seq
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1099	GCATCCCTTTACCTALT	CCTTACAATGAGACGT	TATCAAGGAATCCCTTG cohi_ai1.seq
1101	GCATCGCTTTAGCTAAT	CCTTACAAIGAGACGT	TATCAAGGAATCCCTTG cjblil_ail.seq TATCAAGGAATCCCTTG nem3i6_ail.seq
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150	CTTATAGACCCTTTTAC	CACTAACCAAAAACAA	GGTTTGAGAGAGTATGC cjmin_aii.seq GGTTTGAGAGAGTATGC.agog_aii.seq
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251	TIGGGGTTGATATTCCA	ATTTATECTEGAACATC	CCGAAACTGTGCTTCAG cjb111_a11.seq CCGAAACTGTGCTTCAG nem316_a11.seq
250	TTGGGGTTGATATTCCA	ATTTATECTECAACATC	CCGAAACTGTGCTTCAG nem316_a11.seq
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Alignment Report of AI-WO 2006/078318 method with Weighted residue weight table Thursday, July 29, 2004 5:46 PM AAAGCT CCACTCGCACTTTTCC Majority 6310 6320 6330 6340 6350 A A A G G T A G T G G G C A T T T G G A G G G A A C C A G T C T T C C A G T G G G A G G T T T G T C 2603_ai1.seq 6298 AAAGGTAGTGGGCATTTGGAGGGAACCAGTCTTCCAGTGGGAGGTTTGTC 18rs21_ai1.seq 6067 A A A G G T A G T G G G C A T T T G G A G G G A A C C A G T C T T C C A G T G G G A G G T T T G T C cohi_aii.seq 6299 A A A G G T A G T G G G C A T T T G G A G G G A A C C A G T C T T C C A G T G G G A G G T T T G T C cjblil_ail.seq 6299 A A A G G T A G T G G G C A T T T G G A G G G A A C C A G T C T T C C A G T G G G A G G T T T G T C nem316_a11.seq 6301 A A A G G T A G T G G G C A T T T G G A G G G A A C C A G T C T T C C A G T G G G A G G T T T G T C a909_a11.seq **6300** A A C C C A T T C A G T A C T A C T G C C C A C C G T G G C T T G C C A A C A G C T A G G C T A T Majority 6360 .6370 6380 6390 6400 AACCCATTCAGTACTAACTGCCCACCGTGCCTTGCCAACAGCTAGGCTAT 2603_ail.seq 6348 AACCCATTCAGTACTAACTGCCCACCGTGGCTTGCCAACAGCTAGGCTAT 18rs21_ai1.seq 6117 AACCCATTCAGTACTAACTGCCCACCGTGGCTTGCCAACAGCTAGGCTAT cohl_ail.seq 6349 A A C C C A T T C A G T A C T A C T G C C C A C C G T G G C T T G C C A A C A G C T A G G C T A T cjb111_a11.seq 6349 AACCCATTCACTACTAACTCCCACCGTGCCTTGCCAACAGCTAGGCTAT nem316_ail.seq 6351 AACCCATTCAGTACTACTGCCCACCGTGGCTTGCCAACAGCTAGGCTAT a909_ail.seq 6350 TTACCGACTTAAATAAAGTTAAAAAGGCCAGATTTTCTATGTGACGAAC Majority 6410 6420 · 6430 6440 TTACCGACTTAAATAAAGTTAAAAAGGCCAGATTTTCTATGTGACGAAC 2603_a11.seq 6398 TTACCGACTTAAATAAAGTTAAAAGGCCCAGATTTTCTATGTGACGAAC 18rs21_a11.seq 6167 TTACCGACTTAAATAAAGTTAAAAGGCCAGATTTTCTATGTG'ACGAAC cohl_ail, seq 6399 TTACCGACTTAAATAAAGTTAAAAAGGCCAGATTTTCTATGTGACGAAC cjbiil_ail.seq 6399 TTACCGACTTAAATAAAGTTAAAAAGGCCAGATTTTCTATGTGACGAAC nem316_ail.seq 6401 6400 TTACCGACTTAAATAAAGTTAAAAAAGGCCAGATTTTCTATGTGACGAAC a909_ail.seq A.T.C.A.A.G.G.A.A.C.A.C.T.G.C.C.T.A.C.A.A.G.T.C.G.T.G.T.C.T.A.T.C.A.A.G.T.T.G.T.G.G.A.T.C.C. Majority 6460 6470 6480 6490 ATCAAGGAAACACTTGCCTACAAAGTCGTGTCTATCAAAGTTGTGGATCC 2603_ail.seq 6448 ATCAAGGAAACACTTGCCTACAAAGTCGTGTCTATCAAAGTTGTGGATCC 18rs21_a11.seq 6217 ATCAAGGAAACACTTGCCTACAAAGTCGTGTCTATCAAAGTTGTGGATCC cohlail.seq. 6449 ATCAACGAACACTTCCCTACAAAGTCCTATCAAAGTTCTCCCjbiii ail.seq 6449 A.T C A.A. G A A A C A C T T G C C T A C A A A G T C G T G T C T A T C A A A G T T G T G G A T C C nem316_ai1.seq B451 ATCAAGGAAACACTTGCCTACAAAGTCGTGTCTATCAAAGTTGTGGATCC a909_all.seq 6450 A C A G C T T T A A G T G A G G T T A A G A T T G T C A A T G G T A A G G A T T A T A A C C T Majority 6510 6520 6530 6540 6550 AACAGCTTTAAGTGAGGTTAAGATTGTCAATGGTAAGGATTATATAACCT 2603_ai1.seq 3498 AACAGCTTTAAGTGAGGTTAAGATTGTCAATGGTAAGGATTATATAACCT 18rs21_ai1.seq 5267 -AACAGCTTTAAGTGAGGTTAAGATTGTCAATGGTAAGGATTATATAACCT coh1_ai1.seq 3499 AACAGCTTTAAGTGAGGTTAAGATTGTCAATGGTAAGGATTATATAAACCT cjbii1_ai1.seq 3499 AACAGCTTTAAGTGAGGTTAAGATTGTCAATGGTAAGGATTATATACCT nem316_ai1.seq 5501 AACAGCTTTAAGTGAGGTTAAGATTGTCAATGGTAAGGATTATATAACCT a909_a11.seq 3500 TGCTGACTTGCACACCTTACATCAATCAATCATCGTCTTGGTAAAA Majority 6560 6570 6580 6590 T G C T G A C T T G C A C C T T A C A T G A T C A A T A G T C A T C G T C T C T T G G T A A A A 2603 ail seq TGGTGACTTGCACACCTTACATCATCATCATCGTCTCTTGGTAAAA 18rs21_all.seq :317 TGCTGACTTGCACACCTTACATGATCAATACTCATCGTCTTTTGGTAAAACBULAH.seq 551 T. C. C. T. G. A. C. A. C. C. C. T. A. C. A. T. C. A. 1550 TIGGTGACTTGCACACCCTTACATCATCATACTCATCCTTCTTGGTAAAAAA999a11.seq G G A G A G C G T A T T C C T T A T C A T T C T A C C G A C C G G A A A A G C A C A A C A A C A A C A Majority 6610 6620 6630 6650 G G A G A G C G T A T T C C T T A T G A T T C T A C C G A G G C G G A A A G C A C A A G A A C A 2603_ail.seq 598 G.G.A.G.A.G.C.G.T.A.T.C.C.T.A.T.C.T.A.C.C.G.A.G.C.C.G.A.A.G.C.A.A.G.A.A.A.G.A.A.G.A.A.G.A.A.G.A.A.G.A.A.G.A.A.G.A.A.G.A.A.G.A.A.G.A.A.A.G.A.A.G.A.A.G.A.A.G.A.A.G.A.A.G.A.A.G.A.A.G.A.A.G.A.A.G.A.A.A.G.A.A.G.A.A.G.A.A.G.A.A.G.A.A.G.A.A.G.A.A.G.A.A.A.G.A.A.G.A.A.A.G.A.A.G.A.A.G.A.A.G.A.A.G.A.A.G.A.A.A.G.A.A.G.A.A.A.G.A.A.A.G.A.A.A.G.A.A.A.G.A.A.A.G.A.A.A.G.A.A.A.A.G.A.A.A.G.A.A.A.G.A.A.A.A.G.A.A.A.A.G.A.A.A.A.G.A.A.A.A.G.A.A.A.A.G.A.A.A.A.G.A.A.A.A.G.A.A.A.A.G.A.A.A.A.G.A.A.A.G.A.A.A.G.A.A.A.G.A.A.A.G.A.A.A.G.A.A.A.G.A.A.A.G.A.A.A.G.A.A.A.G.A.A.A.G.A.A.A.G.A.A.A.G.A.A.A.G.A.A.A.G.A.A.A.G.A.A.A.G.A.A.A.G.A.A.A.A.G.A.A.A.G.A.A.A.A.G.A.A.A.A.G.A.A.A.A.G.A.A.A.A.G.A.A.A.A.G.A.A.A.A.G.A.A.A.A.G.A.A.A.G.A.A. 367 GGAGAGCGTATTCCTTATGATTCTACCGAGGCGGAAAAGCACAAAGAACA cohl_ai1.seq :599 G G A G A G C G T A T T.C C T T A T G A T T C T A C C G A G G C G G A A A G C A C A A G A A C A cjb111_a11.seq 1599 G G A G A G C G T A T T C C T T A T G A T T C T A C C G A G G C G G A A A G C A C A A A G A A C A nem316_ail:seq 100 600

Alignment Report of AI-1 \underline{WO} 2006/078318, nethod with Weighted residue weight table. Thursday, July 29, 2004 5:46 PM

AACCGT ACAA ATTA ATCCT TTO FC A GT ATT A GT A G A G A G A G A G A T A C T A C T A G T A T Majority 6660 6670 6680 6690 6700 AACCGTACAAGATTATCGTTTGTCACTAGTGTTGAAGATACTAGTAT 2603_ai1.seq 648 AACCGTACAAGATTATCGTTTGTCACTAGTTTGAAGATACTACTAGTAT 18rs21_ai1.seq 1417 AACCGTACAAGATTATCGTTTGTCACTAGTGTTGAAGATACTAGTAT cohi_ail.seq 649 AACCGTACAAGATTATCGTTTGTCACTAGTCTTCAAGATACTACTAGTAT cjbiii_aii.seq 649 AACCCTACAACATTATCGTTTGTCACTAGTTGAACATACTACTAGTAT nem316_ail.seq 651 AACCGTACAAGATTATCGTTTGTCACTAGTGTTGAAGATACTAGTAT a909_ail.seq 650 6710 6720 6730 6740 6750 698 467 699 699 701 700 CGTCAATAACGATGTTGTGAATGGCTTACTTATCAAATAGGTGACT Majority 6760 6770 6780 6790 6800 748 CGTCAATAACGATGTTGTGAATGGCTTACTT . . . ATCAAATAGGTGACT 2603_ail.seq C G T C A A T A A C G A T G T G T G A A T G G C T T A C T T A C T T A T C A A T A G G T G A C T 18rs21_a11.seq CGTCAATAACGATGTTGTGAATGGCTTACTTACTTATCAAATAGGTGACT cohi_aii.seq 749 CGTCAATAACGATGTTGTGAATGGCTTACTTACTTATCAAATAGGTGACT cjb111_ai1.seq 749 C.C.T.C.A.A.T.A.A.C.G.A.T.G.T.G.A.A.T.G.G.C.T.T.A.C.T.T.A.T.C.A.A.T.A.G.G.T.G.A.C.T. nem316_ai1.seq 751 750 CGTCAATAACGATGTTGTGAATGGCTTACTTACTTATCAAATAGGTGACT a909_aii.seq AATGATGATTGTGAATAATGGTTATCTAGAAGGGAGAAAAATGAAAAAGA Majority 6810 6820 6830 6840 6850 AATGATGATTGTGAATAATGGTTATCTAGAAGGGGAGAAAATGAAAAGA 2603_a11.seq 794 AATGATGATGTGAATAATGGTTATCTAGAAGGGAAAAATGAAAAGA 18rs21_al1.seq 567 AATGATGATTGTGAATAATGGTTATCTAGAAGGGAAAAAATGAAAAGA cohlai1.seq 799 799 AATGATGATTGTGAATAATGGTTATCTAGAAGGGAAAAATGAAAAAGA cjblil ail.seq GACAAAAAAT CGAGAGGGTTATCAGTTACTAATCCTGTCCCAA Majority 6860 6870 6880 6890 .6900 GACAAAAAATATGGAGAGGGTTATCAGTTACTTACTAATCCTGTCCCAA 2603_ai1.seq 344 GACAAAAAATATGGAGAGGGTTATCAGTTACTTTACTAATCCTGTCCCAA 18rs21_ai1.seq 317 GACAAAAATATGGAGAGGGTTATCAGTTACTTACTAATCCTGTCCCAA cohl_ail.seq 349 GACAAAAAATATGGAGAGGGTTATCAGTTACTTACTAATCCTGTCCCAA cjblii_ai1.seq 349 GACAAAAATATGGAGAGGGTTATCAGTTACTTACTAATCCTGTCCCAA nem316_ai1.seq 351 GACAAAAATATGGAGAGGGTTATCAGTTACTTACTAATCCTGTCCCAA a909_ai1.seq 350 ATT CCATT TGGT ATATT GGT A.C A.A.G.G TGA AACCCAA GAT ACCAATCAAGC Majority 6910 . 6920 6930 6940 6950 ATTCCATTCGTATATTGGTACAAGGTGAAACCCAAGATACCAATCAAGC 2603_all.seq 394 67 ATTCCATTCCATTCGTATATTCGTACAAGGTGAAACCCAAGATCAAGC contattseq **399** A C T T G G A A A A G T K A T T G T T A A A A A A C C G G A C A C T G C T A C A C C A T T A G Hajority 6970 .6980 6990 7000 M4. ACTTGGAAAAGTAATTGTTAAAAAAACGGGAGACAATGCTACACCATTAG.2603_ai1.seq ACTTGGAAAAGTAATTGTTAAAAAAACGGGAGACAATGCTACACCATTAG cohi_ai1.seq 149 ACTTGGAAAAGTAATTGTTAAAAAAACGGGAGACAATGCTACACCATTAG cjbiil_ail.seq ACTTGGAAAAGTAATTGTTAAAAAACGGGAGACAATGCTACACCATTAG nem316_a11.seq 151 ACTT GGAAAAGTAATT GTTAAAAAA CGGGGGACAAT GCTACA CCATTAG a909_aii.seq ารถ

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GT GTTAAAAAATGACAATGATAAGTCAGAAACAAGT Majority GCAAAGC GA TTTC 7010 7020 7030 7040 7050 GCAAAGCGACTTTTGTGTTAAAAATGACAATGATAAGTCAGAAACAAGT 2603_ait.seq 5994 3767 GCAAAGCGACTTTTGTGTTTAAAAATGACAATGATAAGTCAGAAACAAGT 18rs21_ai1.seq GCAAAGCGACTTTTGTGTTAAAAATGACAATGATAAGTCAGAAACAAGT cohl_all.seq 5999 GCAAAGCGACTTTTGTGTTAAAAATGACAATGATAAGTCAGAAACAAGT cjbiii_aii.seq 3999 GCAAAGCGACTTTTGTGTTAAAAATGACAATGATAAGTCAGAAACAAGT nem316_ai1.seq 700 t G C A A A G C G A C T T T T G T G T T A A A A A A T G A C A A T G A T A A G T C A G A A A C A A G T a909_a11.seq 7000 CACGAAACGGTAGAGGGTTCTGGAGAAGCATTGAAAACATAAACC Majority 7060 7070 7080 7090 7100 7044 CACGAAACGTAGAGGGTTCTGGAGAACCTTTGAAAAACC 2603_ail.seq 3817 CACGAAACGGTAGAGGGTTCTGGAGAAGCAACCTTTGAAAACATAAAACC 18rs21_a11.seq CACGAAACGGTAGAGGGTTCTGGAGAAGCATTGAAAACATAAACC cohl_ail.seq 7049 CACGAAACGGTAGAGGGTTCTGGAGAAGCAACCTTTGAAAACATAAAACC cjbiii_aii.seq 7049 CACGAAACGGTAGAGGGTTCTGGAGAAGCAACGTTTGAAAACATAAACC nem316_a11.seq 7051 7050 CACGAAACGTAGAGGGTTCTGGAGAAGCATTTGAAAACATAAACC a909_ail.seq TGGAGACTACACATTAAGAGAAAAACAGCACCAATTGGTTATAAAAAAA Majority 7110 7120 7130 . 7140 7150 TGGAGACTACACATTAAGAGAAAAAACAGCACCAATTGGTTATAAAAAAA 2603_ail.seq 7094 TGGAGACTACACATTAAGAGAAACAGCACCAATTGGTTATAAAAAAA 18rs21_ai1.seq TGG AGACTACACATTAAGAGAAACAGCACCAATTGGTTATAAAAAAAChlail.seq TGGAGACTACACATTAAGAGAAGAACAGCACCAATTGGTTATAAAAAA cjbii1_aii.seq TGGAGACTACACATTAAGAGAAAACAGCACCAATTGGTTATAAAAAA nem316_ai1.seq 7101 TGGAGACTACACATTAAGAGAAACAGCACCAATTGGTTATAAAAAAAa909_ail.seq CTGATAAAACCTGGAAAGTTAAAGTTGCAGATAACGGAACAATAATC Majority 7160 7170 7180 7190 7200 CTGATAAAACCTGGAAAGTTAAAGTTGCAGATAACGGAGCAACAATAATC 2603_ai1.seq CTGATAAAACCTGGAAAGTTAAAGTTGCAGATAACGGAACAATAATC 18rs21_ai1.seq CTGATAAACCTGGAAAGTTAAACTTGCAGATAACGGAGCAACAATAATC cohlail.seq 1149 CTGATAAAACCTGGAAAGTTAAAGTTGCAGATAACGGAGCAACAATAATC cjbiii_ati.seq CTGATAAAACCTGGAAAGTTAAAGTTGCAGATAACGGAGCAACAATAATC nem316_ai1.seq CTGATAAACCTGGAAAGTTAAAGTTGCAGATAACGGAACAATAATC a909_ai1.seq GAGGGTATGGATGCAGATAAAGCAGAAACGAAAAGAAGTTTTGAATGC Majority 7210 7220 7230 7240 7250 GAGGGTATGGATGCAGATAAAGCAAGAAAGAAGTTTTGAATGC 2603_a11.seq. 1194 CAGGGTATGGATGCAGATAAAGCAGAGAAAGGAAGTTTTGAATGC 18rs21_ai1.seq 1967 GAGGGTATGGATGCAGATAAAGCAGAAACGAAAAGAAGTTTTGAATGC coh1_ai1.seq 7199 CAGGGTATGGATGCAGATAAAGCAGAGAAAGGAAAGTTTTGAATGC cjbiil_ai1.seq (199 7201 GAGGGTATGGATGCAGATAAAGCAGAAACGAAAAGAAGTTTTCAATGC nem316_ai1.seq CAGGGTATGGATGCAGATAAAGCAGAAACGAAAAGAAGTTTTGAATGC a909_ai1.seq 1200 CCAATATCCAAAATCAGCTATTTATGAGGATACAAAAGAAATTACCCAT Majority 7260 7270 7280 7290 7300 CCAATATCCAAAATCACCTATTTATCAGGATACAAAAGAAATTACCCAT 2603_all.seq CCAATATCCAAAATCAGCTATTTATCAGGATACAAAAGAAATTACCCAT. 18gs21_all.seq CCAATATCCAAAATCACCTATTTATCACGATACAAAAATTACCCAT contail seq 249 C.C.A.A.T.A.T.C.C.A.A.A.T.C.A.G.C.T.A.T.T.A.T.G.A.G.G.A.T.A.C.A.A.A.G.A.A.A.T.T.A.C.C.C.A.T. riem316 at 1. seq. C.C.A.A.T.A.T.C.C.A.A.A.G.A.A.A.T.T.A.C.C.C.A.T. a909 at 1. seq. TAGTTAATGTAGAGGGTTCCAAAGTTGGTGAACAATACAAAGCATTGAAT Majority 7310 7320 .. 7330 🔩 7340 7350 TAGTTAATGTAGGGGTTCCAAAGTTGGTGAACAATACAAAGCATTGAAT 2603_a11.seq 294 TAGTTAATGTAGAGGGTTCCAAAGTTGGTGAACAATACAAAGCATTGAAT 18rs21_ai1.seq TAGTTAATGTAGAGGGTTCCAAAGTTGGTGAACAATACAAAGCATTGAAT coh1_ai1.seq 067 1299 1299 TAGTTAATGTAGAGGGTTCCAAAGTTGGTGAACAATACAAAGCATTGAAT.cjb111_ai1.seq TAGTTAATGTAGAGGGTTCCAAAGTTCGTGAACAATACAAAGCATTGAAT nem316_ail.seq 1301 TAGTTAATGTAGAGGGTTCCAAAGTTGGTGAACAATACAAAGCATTGAAT a909_a11.seq 7300

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Thursday, July 29, 2004 5:46 PM 27, July 29, 2004 5:46 PM CCAATAANA T.C.CAAACATCTCCTCTAACTTCCTAACTTCCTCAACCTTCCTAATC 7370 7380 7390 7400 7344 7117 7349 CCAATAAATGGAAAAGATGGTCGAAGAGAGATTGCT.GAAGGTTGGTTATC cjb111_ai1.seq 7410 7420 7430 7440 7450 A A A A A A A T T A C A G G G G T C A A T G A T C T C G A T A A G A A T A A A A T T G 2603_all.seq 7394 AAAAAAATTACAGGGGTCAATGATCTCGATAAGAATATAAAATTG 18rs21_ai1.seq **1167** AAAAAAAAATACAGGGGTCAATGATCTCGATAAGAATAAAAATTG coh1_a11.seq AAAAAAATTACAGGGGTCAATGATCTCGATAAGAATAAAAATTC cjb111_a11.seq AAAAAAATTACAGGGGTCAATGATCTCGATAAGAATAAAAATTG nem316_ai1.seq AAAAAAATTACAGGGGTCAATGATCTCGATAAGAATATAAAATTG a909_a11.seq A A T T A A C T G T T G A G G G T A A A A C C A C T G T T G A A A C G A A G A A C T T A A T C A A Majority 7470 7480 7490 7500 AATTAACTGTTGAGGGTAAAACCACTGTTGAAACGAAAGAACTTAATCAA 2603.aii.seq 444 AATTAACTGTTGAGGGTAAAACCACTGTTGAAACGAAAGAACTTAATCAA 18rs21_a11:seq 217 449 AATTAACTGTTGAGGGTAAAACCACTGTTGAAACGAAAGTAATCAA coh1_ai1.seq AATTAACTGTTGAGGGTAAAACCACTGTTGAAACGAAAGAACTTAATCAA cjbii1_ai1.seq 449 AATTAACTGTTGAGGGTAAAACCACTGTTGAAACGAAAGAACTTAATCAA nem316_a11.seq 451 450 CCACTAGATGTCGTTGTGCTATTAGATAATTCAAATAGTATGAATAATGA Majority 7510 7520 7530 7540 7550 CCACTAGATGTCGTTGTGCTATTAGATAATTCAAATAGTATGAATAATGA 2603_ai1.seq 494 CCACTAGATGTCGTTGTGCTATTAGATACTTCAAATAGTATGAATAATGA 18rs21_aif.seq 267 CCACTAGATGTCGTTGTGCTATTAGATAATTCAAATAGTATGAATAATGA cohlail.seq 499 CCACTAGATGTCGTTGTGCTATTAGATAGTTCAAATAGTATGAATAATGA cjbiil ail.seq 499 CCACTAGATGTCGTTGTGCTATTAGATAATTCAAATAGTATGAATAATGA nem316_ai1.seq 501 CCACTAGATGTCGTTGTGCTATTAGATACTTCAAATAGTATGAATAATGA a909_ail.seq A C A C C C A A T A A T T C T C A A A G A G C A T T A A A A G C T G G G G A A G C A G T T G A A A Majority 7570 7580 7590 7600 AAGAGCCAATAATTCTCAAAGAGCATTAAAAGCTGGGAAGCAGTTGAAA 2603_ai1.seq 317 AAGAGCCAATAATTCTCAAAGAGCATTAAAAGCTGGGGAAGCAGTTGAAA 18rs21_ai1.seq AAGAGCCAATAATTCTCAAAGAGCATTAAAAGCTGGGGAAGCAGTTGAAA cohl_ail.seq 549 AAGAGCCAATAATTCTCAAAGAGCATTAAAAGCTGGGGAAGCAGTTGAAA cjb111_a11.seq AAGAGCCAATAATTCTCAAAGAGCATTAAAAGCTGGGGAAGCAGTTGAAA nem316_ai1.seq 551 AAGAGCCAATAATTCTCAAAGAGCATTAAAAGCTGGGGAAGCAGTTGAAA a909_ail_seq A G C T G A T T G A T A A A A T T A C A T C A A A T A A A G A C A A T A GTAGCTCTTGTG Majority 7610 7620 7630 7640 7650 AGCTGATTGATAAAATTACATAAAAGACAAATAGACTAGCTCTTGTG.2603_a11.seq A G C T G A T T G A T A A A A T T A C A T C A A A T A A G A C A A T A G A C T A G C T C T T G T C 18rs21 at 1 seq 367 AGCTGATTGATAAAATTACATCAAATAAAGACAATAGAGTAGCTTGTGCONLailseg 599 A G C T G A T T G A T A A A A T T A C A T G A A A T A A A G A C A A T A G A G T A G G T C T T G T G C BILL att. seq 599 501. A G G T G A T T G A T A A A A T T A C A T C A A A T A A A G A C A A T A G A G T A G G T G T G T G T G nem316 att seq AGCTGATTGATAAAATTACATCAAATAAAGACAATAGACTAGCTCTTGTG ag00 all seq A C A T A T G C C T C A A C C A T T T T T G A T G G T A C T G A A G C G A C C G T A T G A A A G G G RAJocity 7660 . 7670 7680 7690 A.CATATGCCTCAACCATTTTTGATGGTACTGAAGCGGACCGTATCAAAGGGC2603_ail.seq 644 A CATATGCCTCAACCATTTTTGATGGTACTGAAGCGACCGTATCAAAGGG 18rs21_ai1.seq 417 ACATATGCCTCAACCATTTTTGATGGTACTGAAGCGACCGTATCAAAGGG cohilail.seq A CATAT G C CT CAA C CATTTTT GAT G G T A CT G A A G C G A C C G T A T C A A A G G G c jbiii_aii.seq. ACATATGCCTCAACCATTTTTGATGGTACTGAAGCGACCGTATCAAAGGG nem316_ai1.seq

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TTAACARATGATGCT		ATTCTAAAGTCAAGAATTC	CAAA 2603_aii.seq									
TTAACAAATGATGCT		ATTCTAAAGTCAAGAATTC	CAAA 18rs21_a11.seq									
TTAACAAATGATGCT	'A'A C G A A G T T A A T	ATTOTALACTOLLORATE	CAAA cohl_ail.seq									
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CCAACCCCACCATAT	AAATGGGGATCG	CACGCTCTATCAATTTGGT	G C G A 2603_ail.seq									
CCAACCCCAGCATAT	AAATGGGGATCG	CACGCTCTATCAATTTGGT	G C G A 18rs21_all.seq									
		CACGCTCTATCAATTTGGT	G C G A cohl_ail.seq									
GGA'AGCGGAGCATAT	AAAIGGGAIGG	CACCCTATCAATTTCGT	G C G A cjb111_ai1.seq									
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Alignment Report of Al-1_augmment, using J. Hern method with Weighted residue weight table.

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CT/US2005/027239

Alignment Report of Al-1 WO 2006/078318
Thursday, July 29, 2004 5:46 PM

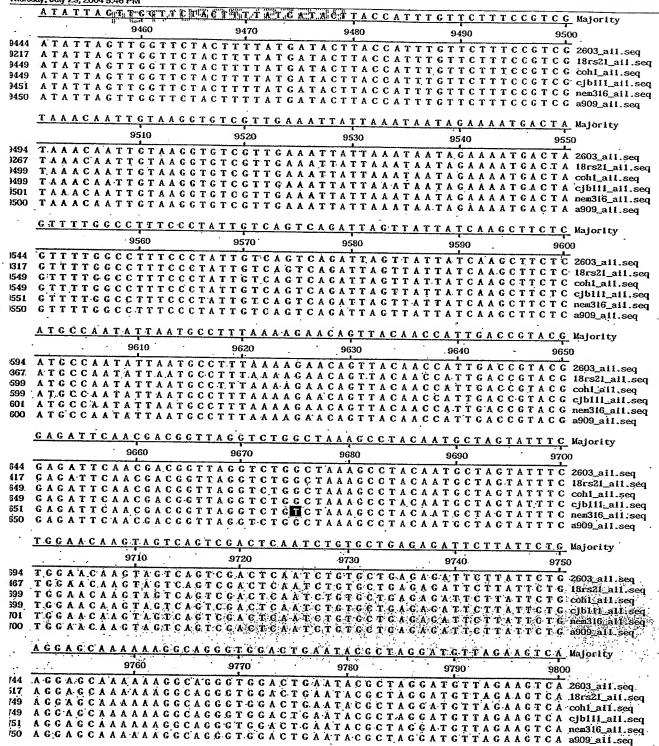
AATCCA AATATA'ACACCACCAA'A'AICGTTTAT CA CATTTTTACTGTTGGGATTGG Majority 8410 8430. 8440 AATGGAAATATAAGACCTAAAGGTTATGACATTTTTACTGTTGGGATTGG 2603_ai1.seq 8394 AATGGAAATATAAGACCTAAAGGTTATGACATTTTTACTGTTGGGATTGG 18rs21_ai1.seq 8167 AATGGAAATATAAGACCTAAAGGTTATGACATTTTTACTGTTGGGATTGG cohl_ai1.seq **83**99 AATGGAAATATAAGACCTAAAGGTTATGACATTTTTACTGTTGGGATTGG cjb111_a11.seq **B399** AATGGAAATATAAGACCTAAAGGTTATGACATTTTTACTGTTGGGATTGG nem316_ai1.seq 8401 8400 AATGGAAATATAAGACCTAAAGGTTATGACATTTTTACTCTTTGGGATTGG a909_ail.seq TGTAAACGGAGATCCTGCAACTCCTCTTGAAGCTGAGAATTTATGC Majority 8460 8470 8480 8490 8500 TGTAAACGCAGATCCTGGTGCAACTCCTCTTGAAGCTGAGAATTTATGC 2603_ail.seq **B444** TGTAAACGGAGATCCTGGTGCAACTCCTCTTGAAGCTGAGAAATTTATGC 18rs21_ail.seq **B217** TGTAAACGGAGATCCTGGTGCAACTCCTCTTGAAGCTGAGAAATTTATGC cohl_a11.seq **B449** TGTAAACGGAGATCCTGGTGCAACTCCTCTTGAAGCTGAGAATTTATGC cjb111_ai1.seq **B449** TGTAAACGGAGATCCTGGTGCAACTCCTCTTGAAGCTGAGAATTTATGC nem316_a11.seq B451 TGTAAACGGAGATCCTGGTGCAACTCCTTGAAGCTGAGAATTTATGC a909_ail.seq B450 AATCAATATCAAGTAAAAAAATTATACTAATGTTGATGATACAAAT Majority 8510 8520 8530 8540 8550 AATCAATATCAAGTAAAACAGAAAATTATACTAATGTTGATGATACAAAT 2603_aii.seq 8494 **B267** AATCAATATCAAGTAAAACAGAAAATTATACTAATGTTGATGATACAAAT 18rs21_a11.seq AATCAATATCAAGTAAAACAGAAAATTATACTAATGTTGATGATACAAAT cohl_ail.seq. AATCAATATCAAGTAAAACAGAAAATTATACTAATGTTGATGATACAAAT cjblil_ail.seq A.A.T.C.A.A.T.A.T.C.A.A.G.T.A.A.A.C.A.G.A.A.A.T.T.A.T.A.C.T.A.A.T.G.T.T.G.A.T.G.A.T.A.C.A.A.A.T. nem316_a11.seq 3501 **3500** AATCAATATCAAGTAAAACAGAAAATTATACTAATGTTGATGATACAAAT a909_ail.seq AAAATTTATGATGAGCTAAATAAATACTTTAAAACAATTGTTGAGGAAAA Majority 8570 · 8580 8590 . . 8600 AAAATTTATGATGAGGTAAATAATACTTTAAAACAATTGTTGAGGAAAA 2603_aii.seq 3544 AAAATTTATGATGAGCTAAATAAATACTTTAAAACAATTGTTGAGGAAAA 18rs21_ai1.seq 3317 AAAATT TATGAT GAGCTAAATAAATACTTTAAAACAATTGTT GAGGAAAA cohla11.seq AAAATTTATGATGAGCTAAATACTTTAAAACAATTGTTGAGGAAAA cjb111_a11.seq AAAATTTATGATGAGCTAAATAAATACTTTAAAACAATTGTTGAGGAAAA nem316_ail.seq AAAATTTATGATGAGCTAAATAAATACTTTAAAACAATTGTTGAGGAAAA a909_ail.seq ACATTCTATTGTTGATGCAAATGTGACTGATCCTATGGGAAGATGATTG Majority 8610 8620 8630 8640 ACATTCTATTGTTGATGGAAATGTGACTGATCCTATGGGAGAGATGATTG 2603_ai1.seq 1594 1367 ACATTCTATTGTTGATGGAAATGTGACTGATCCTATGGGAAGATGATTG 18rs21_ail.seq ACATTCTATTGTTGATGGAAATGTGACTGATCCTATGGGAGAGATGATTG cohl_ail.seq 1599 . ACATTCTATTGTTGATGGAAATGTGACTGATCCTATGGGAGAGATGATTG cjbiil_aif.seq 1599 ACATTCTATTGTTGATGGAAATGTGACTGATCCTATGGGAAGATGATTG nem316_a11.seq 1601 ACATTCTATTGTTGATGGAAATGTGACTGATCCTATGGGAAGATGATTG a909_ail.seq 1600 AATTCCAATTAAAAATGGTCAAAGTTTTACACATGATGATTACGTTTTC Majority 8670 8680 8690 8700 AATTCCAATTAAAAATGCTCAAAGTTTTACACATGATGATTACGTTTTC 2603 ail seq AATTCCAATTAAAAATGCTCAAACTTTTACACATGATGATTACGTTTTTC 181521 ail seq 417. AATTCCAATTAAAAAATGGTCAAAGTTTTACACATGATCATTACGTTTTC contail seq 649 649 AATTCCAATTAAAAAATGGTCAAAGTTTTACACATGATGATTACGTTTTC cjbiil ali seq 651 AATTCCAATTAAAAAATGGTCAAAGTTTTACACATGATGATTACGTTTTC cibiil ali seq 650 AATTCCAATTAAAAAATGGTCAAAGTTTTTACACATGATGATTACGTTTTC a909/ail seq 8720 . 8730. 8710 8740 694 GTTGCAAATGATCCCACTCAATTAAAAATGGTGTGGCTCTTGGTGCACC 2603_a11.seq GTTGGAAATGATGGCAATTAAAAAATGGTGTGGCTCTTTGGTGCACC 18,521_a11.seq 699 GTTGGAAATGATGGCAGTCAATTAAAAATGGTGTGTGTCTTGGTGGCCCcohlall.seq GTTGGAAATGATGGCAGTCAATTAAAAAATGGTGGCTCTTGGTGGACC cjbiii_aii.seq 699 GTTGGAAATGATGGCAGTCAATTAAAAAATGGTGTGGCTCTTGGTGGACC nen316_a11.seq 701 GTT G G A A A T G A T G G C A G T C A A T T A A A A A T G G T G G C T C T T G G T G G A C C a909_ai1, seq :700

Alignment Report of Al-WO 2006/078318 Thursday, July 29, 2004 5:46 PM AAACAGFEGATIGE CECALATTTT TAAANA GATGTTACAGTGACTTATGATAAGA Majority 8760 8770 8780 8790 8800 8744 AAACAGTGATGGGGGAATTTTAAAAGATGTTACAGTGACTTATGATAAGA 2603_ai1.seq AAACAGTGATGGGGGAATTTTAAAAGATGTTACAGTGACTTATGATAAGA 18rs21_ai1.seq 8749 AAACAGTGATGGGGGAATTTTAAAAGATGTTACAGTGACTTATGATAAGA cjbiii_ail.seq 8749 AAACAGTGATGGGGGGAATTTTAAAAGATGTTACAGTGACTTATGATAAGA nem316_ai1.seq 8751 8750 CATCTCAAACCATCAAATCAATTCATTTCAACTTAGGAAGTGGACAAAA Majority 8810 8820 8830 8840 8850 CATCTCAAACCATCAAATCAATTGAACTTAGGAAGTGGACAAAAA 2603, ai1.seq 8794 CATCTCAAACCATCAAAATCAATCATTTGAACTTAGGAAGTGGACAAAAA 18rs21_a11.seq 8567 CATCTCAAACCATCAAATCAATTTGAACTTAGGAAGTGGACAAAAA cohlail.seq. 8799 CATCTCAAACCATCAAATCAATCATTTGAACTTAGGAAGTGGACAAAAA cjb111_ai1.seq 8799 CATCTCAAACCATCAAATCAATCATTTGAACTTAGGAAGTGGACAAAAA nem316_ai1.seq 8801 CATCTCAAACCATCAAATCAATTTTGAACTTAGGAAGTGGACAAAAA a909_ai1.seq 8800 GTAGTTCTTACCTATGATGTACGTTTAAAAGATAACTATATAAGTAACAA Majority 8860 8870 8880 8890 8900 GTAGTTCTT.ACCTATGATGTACGTTTAAAAGATAACTATAAAGTAACAA 2603_aii.seq **B844** GTAGTTCTTACCTATGATGTACGTTTAAAAGATAACTATATAAGTAACAA 18rs21_ai1.seq GTAGTTCTTACCTATGATGTACGTTTAAAAGATAACTATATAAGTAACAA cohlail.seq **B849** GTAGTTCTTACCTATGATGTACGTTTAAAAGATAACTATAAGTAA'CAA cjbiil ail seq GTAGTTCTTACCTATGATGTACGTTTAAAAGATAACTATATAAGTAACAA nem316_ai1.seq GTAGTTCTTACCTATGATGTACGTTTAAAAGATAACTATAAAGTAACAA a909_aii.seq ATTTTACAATACAAATAATCGTACAACGCTAAGTCCGAAGAGTGAAAAG Majority 8910 8920 8930 8940 8950 8894 ATTTTACAATACAAATCGTACAACGCTAAGTCCGAAGAGTGAAAAAG 2603_ai1.seq ATTTTACAATACAAATAATCGTACAACGCTAAGTCCGAAGACTGAAAAAG 18rs21_ai1.seq ATTTTACAATACAAATAATCGTACAACGCTAAGTCCGAAGAGTGAAAAAAC cohla11.seq ATTTTACAATACAAATCGTACAACCCTAAGTCCGAAGAGTGAAAAACcjb111_ai1.seq ATTTTACAATACAAATCGTACAACGCTAAGTCCGAAGAGTGAAAAG nem316_ai1.seq ATTTTACAATACAAATCGTACAACGCTAAGTCCGAAGAGTGAAAAAG a909_aii.seq ACCAAATACTATTCGTGATTTCCCAAATTCCCAAAATTCGTGATGTTCGT Majority 8960 8970 8980 8990 9000 AACCAAATACTATTCGTGATTTCCCAAATTCCCAAAATTCGTGATGTTCGT 2603_ai1.seq 3944 AACCAAATACTATTCGTGATTTCCCAAATTCCCAAAATTCGTGATGTTCGT 18rs21_ai1.seq 3717 AACCAAATACTATTCGTCATTTCCCAAATTCCCAAAATTCGTGATGTTCGT coh1_ai1.seq 3949 AACCAAATACTATTCGTGATTTCCCAAATTCCCAAAATTCGTGATGTTCGT cjb111_a11.seq 3949 AACCAAATACTATTCGTGATTTCCCAAATTCCCAAAATTCGTGATGTTCGT nem316_ai1.seq 3951 AACCAAATACTATTCGTGATTTCCCAATTCCCAAAATTCGTGATGTTCGT a909_a11.seq 3950 GAGTTTCCGGTACTAACCATCAGTAATCAGAAGAAATGGGTGAGGTTGA Majorlty 9010 9020 9030 9040 9050 GAGTTTCCGGTACTAACCATCAGTAATCAGAAGAAAATGGGTGAGCTTGA 2603 ail.seq.GAGTTTCCGGTAACTAACCATCAGTAATCAGAAGAAATGGGTGAGGTTGA 18rs21 ail.seq GAGTTTCCCGGTACTAACCATCAGTAATCAGAAAATGGGTGACGTTGA.coht.all.seq: GAGTTTCCGGCTACTAACCATAATCACAAAATCCCAAAATCCCACTTCACDIIL all seq GAGTTTCCCGGTACTAACCATCACTAATCACAAAATCGCTTGACCTTGACCTTGA DOO GAGTTTCCGGTACTACCATCACTAATCACTAAGAAGAAATGGGTTGAGTTGA ATTTATTA AAGTTAATAATGACAAACATTCAGAATCGCTTTTGGGGACCTA Hajority 9060 9070 9080 9090. . 9100 ATTTATTAAAGTTAATAAAGACAAACATTCAGAATCGCTTTTGGGAGCTA 2603_ail.seq 1044 ATTTATTAAAGTTAATAAAGACAAACATTCAGAATCGCTTTTGGGGAGCTA ifirs21_ati.seq **1817** ATTTATTAAAGTTAATAAAGACAAACATTCAGAAATCGCTTTTGGGGAGCTA cohl_ail.seq 1049 ATTTATTAAAAGTTAAATAAAGACAAACATTCAGAATCGCTTTTGGGAAGCTA cjb111_a11.seq 1049 ATTTATTAGGGAGCTAAAAGACAATCAGAATCGCTTTTGGGAGCTA.nem316_a11.seq 1051 ATTTATTAAAGTTAATAAAGACAAACATTCAGAATCGCTTTTGGGAGCTA a909_a11.seq

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Alignment Report of Al-1 $\underline{WO}~2006/078318$ method with Weighted residue weight table. Thursday, July 29, 2004 5:46 PM

AGTTTC X A C TIT C A C A TI A C A A A A A A A C A TIT TTTCTGGGTATAAGCAATTTGTT Majority 9110 9120 9130 9140 9150 AGTTTCAACTTCAGATAGAAAAGATTTTTCTGGGTATAAGCAATTTGTT 2603_ail.seq 9094 8867 AGTTTCAACTTCAGATAGAAAAAGATTTTTCTGGGTATAAGCAATTTGTT 18rs21_ai1.seq AGTTTCAACTTCAGATAGAAAAGATTTTTCTGGGTATAAGCAATTTGTT cohl_ail.'seq 9099 A G T T T C A A C T T C A G A T A G A A A A G A T T T T T C T G G G T A T A A G C A A T T T G T T cjb111_ai1.seq 9099 AGTTTCAACTTCAGATAGAAAAGATTTTTCTGGGTATAAGCAATTTGTT nem316_ai1.seq 9101 AGTTTCAACTTCAGATAGAAAAGATTTTTCTGGGTATAAGCAATTTGTT a909_a11.seq 9100 9160 . 9170 9180 9190 9200 **B144** CCAGAGGGGAAGTGATGTTACAACAAAGAATGAT.GGTAAAATTTATTTAA 18rs21_a11.seq B917 9149 **B149** 9151 9150 A.G.C.A.C.T.T.C.A.A.G.T.C.C.T.A.T.A.A.T.T.A.T.G.A.A.T.T.T.C.A.A.G.T.C.C.A.G.A.T.C. Majority 921Ô 9220 9230 9240 . 9250 AGCACTTCAAGATGGTAACTATAAATTATGAAATTTCAAGTCCAGATC 2603_aii.seq 1194 AGCACTTCAAGATGGTAACTATAAATTATTGAAATTTCAAGTCCAGATG 18rs21_a11.seq 1967 A G.C A.C T T C A A G A T G G T A A C T A T A A A T T A T A T G A A A T T T C A A G T C C A G A T G. cohl_aif.seq 1199 A G C A C T T C A A C A T G G T A A C T A T A A A T T A T A T G A A A T T T C A A G T C C A G A T G cjbiii_aii.seq 1199 AGCACTTCAAGATGGTAACTATAAATTATCAAATTCAAGTCCAGATG nem316_ail.seq 1201 AGCACTTCAAGATGGTAACTATAAATTATGAAATTTCAAGTCCAGATG a909_aii.seq 1200 G C T A T A T A G A G G T T A A A A C C A A A C C T G T T G T C A C A T T T A C A A T T C A A A A T Majority 9260 9270 9280 9290 9300 244 GCTATATAGAGGTTAAAACGAAACCTGTTGTGACATTTACAAATTCAAAAT 2603_a11.seq 1017 . G C T A T A T A G A G G T T A A A A C G A A A C C T G T T G T G A C A T T T A C A A T T C A A A A T 18rs21_ail.seq G C T A T A T A G A G G T T A A A A C G A A A C C T C T T G T G A C A T T T A C A A T T C A A A A T cohl_ail.seq G C T A T A G A G G T T A A A A C G A A A C C T G T T G T G A C A T T T A C A A T T C A A A A T cjb111_ail.seq GCTATATAGAGGTTAAAACGAAACCTGTTGTGACATTTACAAATTCAAAAT nem316_ail.seq 251 GCTATATAGAGGTTAAAACGAAACCTGTTGTGAGATTTACAAATTCAAAAT a909_ail.seq 1250 G G A G A A G T T A C G A A C C T G A A A G C A G A T C C A A A T G C T A A T A A A A T C A A A T Majority 9310 9320 9340 GGAGAAGTTACGAACCTGAAAGCAGATCCAAAT.GCTAATAAAAAT.CAAAT 2603_ai1.seq 294 G G A G A A G T T A C G A A C C T G A A A G C A G A T C C A A A T G C T A A T A A A A T C A A A T 18rsZi_ail.seq 067 G G A G A A G T T A C G A A C C T G A A A G C A G A T C C A A A T G C T A A T A A A A T C A A A T cohi_ail.seq 299 G G A G A A G T T A C G A A C C T G A A A G C A G A T C C A A A T G C T A A T A A A A T C A A A T cjbiii_aii.seq 299 G G A G A A G T T A C G A A C C T G A A A G C A G A T C C A A A T G C T A A T A A A A T C A A A T nem316_ai1.seq 301 G G A G A A G T T A C C A A C C T G A A A G C A G A T C C A A A T G C T A A T A A A A T C A A A T a909_ai1.seq 300 CGGGTATCTTGAAGGAAATGGTAAACATCTTATTACCAACACTCCCAAAC Majority 9360 9370 . 9380 9390 9400 344 C.G.G.G.T.A.T.C.T.T.C.A.A.G.G.A.A.T.G.G.T.A.A.A.C.A.T.C.T.T.A.C.C.A.A.C.A.C.T.C.C.C.A.A.C. 18rs21 at 1. seq 117 CGGGTATCTTGAAGGAAATGGTAAACATCTTATTACCAACACTCCAAAC 349 CGGGTATCTTGAAGGAAATGGTAAACATCTTATTACCAACACTCCCAAAC 349 351 CG GG TATCTTGAAGGAAATGGTAAACATCTTATTACCAACACTCCCAAAC nem316 all seq GCCCACCAGGTGTTTTCCTAAAACAGGGGGAATTGGTACAATTGTCTAT Majority 9410 9420 9430 9440 9450 GCCCACCAGGTGTTTTCCTAAAACAGGGGGAATTGGTACAATTGTCTAT 2603_ail.seq 167 G.C.C.C.A.C.C.A.G.G.T.G.T.T.T.T.C.C.T.A.A.A.C.A.G.G.G.G.G.A.T.T.G.G.T.A.C.A.A.T.T.G.T.C.T.A.T. 18rs21_ail.seq G C C A C C A G C T G T T T T C C T A A A A C A G G G G G A A T T G G T A C A A T T G T C T A T cohi_aii.seq 199 GCCCACCAGGTGTTTTTCCTAAAACAGGGGGAATTGGTACAATTGTCTAT cjb111_a11.seq 199 GCCCACCAGGTGTTTTCCTAAAACAGGGGGAATTGGTACAATTGTCTAT nem316_ai1.seq 101 GCCCACCAGGTGTTTTTCCTAAAACAGGGGGAATTGGTAAAATTGTCTAT a909_a11.seq 100



AY, JUNY 29, 2004 5:46 PM CAGAGCA GCA GCATT GATT GATT GATT GATT CCAAAAAA TCAAATCAGGATTTACCA MAJORITY 9820 9830 9840 GAGAGCAGGTTGACCATGTGATCAATTCAAATCAGGATTTACCA 2603_ail.seq 794 1567 1799 1799 CAGAGCAGGTTGACCATGTGATCCAAAAAATCAATCAGGATTTACCA nem316_ai1.seq 1801 CAGAGCAGGTTGACCATGTGATCAATCAAAAATCAATCAGGATTTACCA a909_a11.seq 1800 ATCTACCCTGGTTCAGAAGAGGACAATCTGCAACGGGGAGTTGGTCATCT Majority 9860 9870 9880 9890 9900 ATCTACCCTGGTTCAGAAGAGGACAATCTGCAACGGGGAGTTGGTCATCT 2603_ail.seq 1844 ATCTACGCTGGTTCAGAAGAGGACAATCTGCAACGGGGAGTTGGTCATCT 18rs21_a11.seq 1617 ATCTACGCTGGTTCAGAAGAGGACAATCTGCAACGGGGAGTTGGTCATCT cohl_aii.seq 1849 ATCTACGCTGGTTCAGAAGAGGACAATCTGCAACGGGGAGTTGGTCATCT cjb111_ai1.seq RAG ATCTACGCTGGT CAGAAGAGGACAATCTGCAACGGGGAGTTGGTCATCT nem316_ail.seq 1851 ATCTACGCTGGTTCAGAAGAGGACAATCTGCAACGGGGAGTTGGTCATCT a909_ail.seq 1850 A G A A G G G A T A A G T T T G C C G A T T G G A G G G C T T C T A C A C A T G C G G T C T T G A Majority 9910 9920 9930 9940 9950 AGAAGGGATAAGTTTGCCGATTGGAGGGGCTTCTACACATGCGGTCTTGA 2603_ai1.seq 1894 AGAAGGGATAAGTTTGCCGATTGGAGGGGCTTCTACACATGCGGTCTTGA 18rs21_ai1.seq AGAAGGGATAAGTTTGCCGATTGGAGGGGCTTCTACACATGCGGTCTTGA cohi_ai1.seq A G A A G G G A T A A G T T T G C C G A T T G G A G G G G C T T C T A C A C A T G C G G T C T T G A cjb111_a11.seq AGAAGGGATAAGTTTGCCGATTGGAGGGGCTTCTACACATGCGGTCTTGA nem316_ail.seq 901 A G A A G G G A T A A G T T T G C C G A T T G G A G G G G C T T C T A C A C A T G C G G T C T T G A a909_ai1.seq **90**0 GCGGTCAAAGAGGTATGCCAGCTGCTCGGTTGTTTGCGGATTTGGATAAG Majority 9960 9970 9980 9990 10000 GCGGTCAAAGAGGTATGCCAGCTGCTCGGTTGTTTGCGGATTTGGATAAG 2603_ail.seq GCGGTCAAAGAGGTATGCCAGCTGCTCGGTTGTTTGCGGATTTGGATAAG 18rs21_ail.seq GCGGTCAAAGAGGTATGCCAGCTGCTCGGTTGTTTGCGGATTTGGATAAG cohlail.seq GCGGTCAAAGAGGTATGTCAGCTGCTCGGTTGTTTGCGGATTTGGATAAG cjbill_aii.seq GCGGTCAAAGAGGTATGTCAGCTGCTCGGTTGTTTGCGATTTGGATAAG a909_ai1.seq ATGAAAAAGGTGATTATTTTATGTTACCAATCTGAAAGAACCTTGGC Majority 10010 10020 10030 10040 10050 ATGAAAAAGGTGATTATTTTTTATGTTACCAATCTGAAAGAACCTTGGC 2603_ai1.seq 994 ATGAAAAAGGTGATTATTTTTATGTTACCAATCTGAAAGAACCTTGGC 18rs21_a11.seq 767 ATGAAAAAGGTGATTATTTTTATGTTACCAATCTGAAAGAACCTTGGC cohlail.seq 999 ATGAAAAAGGTGATTATTTTTATGTTACCAATCTGAAAGAACCTTGGC cjb111_ai1.seq 0001 ATGAAAAAGGTGATTATTTTATGTTACCAATCTGAAAGAACCTTGGC nem316_ai1.seq TTATCAAGTGGATCGTATCATGGTGATTGAACCTAGCCAATTGGCCG Majority 10060 10070 10080 10090 · 10100 DO44 TTATCAAGTGGATGGTATCATGGTGATTGAACCTAGCCAATTGGATGCCG 2603 all seq DO49 TTATCAAGTGGATGGTATCATGGTGATTGAACCTAGCGAATTGGCATGGCGGCGG DO49 TTATCAAGTGGATCGTATCATGGTGATTGAAGCCTAGCCAATTGGATGCCG DOSI TTATCAAGTGGATCGTATCATGGTGATTGAACCTAACCAATTGGATGCCG DOSO TTATCAAGTGGATGGTATCATGGTGATTGAACCTAGCCAATTGGATGCCCAGOD ALL Seq T G A G C A T T G A A G A C C A T A A A G A T T A T G T T A C C C T T C T G A C C T A C A C C T Hajority 10120 10110 10130 • . .. 10140 :10150 DO94 T.G.A.G.C.A.T.T.G.A.A.G.A.G.G.A.T.A.A.A.G.A.T.T.A.T.G.T.T.A.C.C.C.T.T.C.T.G.A.C.C.T.G.T.A.C.A.C.C.T. 2603_at1.seq B67 TGAGCATTGAAGAGGATAAAGATTATGTTACCCTTCTGACCTGTACACCT 18rs21 all seq DO99 TGAGCATTGAAGAGGATAAAGATTATGTTACCCTTCTGACCTGTACACCT cohi/aii.seq DO99 TGAGCATTGAAGAGGATAAAGATTATGTTACCCTTCTGACCTGTACACCT cjb111_all.seq DIOI T.G.A.G.C.A.T.T.G.A.A.G.A.T.A.A.G.A.T.T.A.T.G.T.T.A.C.C.C.T.T.C.T.G.A.C.C.T.G.T.A.C.A.C.C.T. nem316_aii.seq DIOO: TGAGCATTGAAGAGGATAAAGATTATGTTACCCTTCTGACCTGTACACCT a909_ai1.seq

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Alignment Report of Al-1_alignment, using J. Hein method with Weighted residue weight table. Thursday, July 29, 2004 5:46 PM Thursday, July 29, 2004 5:46 PM TATACCCA RECTCATCTCAGAAAACTTTTATACCTCA Majority TAAAGGTGTT 10510 10494 TAAAGGTCGTTATAATAGCGGAGCTCATCTGAGAAAACTTTTATACCTCA 2603_ail.seq 10267 TAAAGGTCGTTATAATAGCGGAGCTCATCTGAGAAAACTTTTATACCTCA 18rs21_ai1.seq 10499 TAAAGGTCGTTATAATAGCGGAGCTCATCTGAGAAACTTTTATACCTCA cohi_aii.seq 10499 TAAAGCTCGTTATAATAGCGGAGCTCATCTGAGAAAACTTTTATACCTCA cjb111_ai1.seq 10501 TAAAGGTCGTTATAATAGCGGAGCTCATCTGAGAAAACTTTTATACCTCA nem316_ail.seq 10500 TAAAGGTCGTTATAATAGCGGAGCTCATCTGAGAAAACTTTTATACCTCA a909_aii.seq A.G.T.C.A.G.T.C.T.A.G.C.T.T.G.A.T.C.A.T.G.A.G.C.C.A.T.T.A.G.G.A.G.T.T.A.T.C.C.T.T.A.T.C. Majority 10560 10570 10580 10590 10544 AAGTCAGTCTAGCTTTGATATCATGAAGCCATTAGGAGTTATTCCTTATC 2603_ai1.seq 10317 A A G T C A G T C T A G C T T T G A T A T C A T G A A G C C A T T A G G A G T T A T C C T T A T C 18rs21_ai1.seq 10549 AAGTCAGTCTAGCTTTGATATCATGAAGCCATTAGGAGTTATTCCTTATC cohlail.seq 10549 AAGTCAGTCTAGCTTTGATATCATGAAGCCATTAGGAGTTATTCCTTATC cjb111_ai1.seq 10551 AAGTCAGTCTAGCTTTGATATCATGAAGCCATTAGGAGTTATTCCTTATC nem316_ail.seq 10550 AAGTCAGTCTAGCTTTGATATCATGAAGCCATTAGGAGTTATTCCTTATC a909_all.seq TTTTAGTGGCGCGCGATCCATATAGTGATAGATCGAGATATTTAGATCCA Majority 10620 10630 10640 10594 TTTTAGTGGCGCGCGATCCATATAGTGATAGATCGAGATATTTAGATCCA 2603_ai1.seq . 10367 TTTTAGTGGCGCGCGATCCATATAGTGATAGATCGAGATATTTAGATCCA 18rs21_all.seq 10599 TTTTAGTGGGGGGGGATCCATATAGTGATAGATCGAGATATTTAGATCCA cohlail.seq TTTTAGTGGCGCGCGATCCATATAGTGATAGATCGAGATATTTAGATCCA cjbili_aii.seq 10599 10601 T.TTTAGTGGCGCGCGAT.CCATATAGTGATAGATCGAGATATTTAGATCGA nem316_ai1.seq TTTTAGTGGCGCGCGATCCATATAGTGATAGATCGAGATATTTAGATCCA a909_ail.seq 10600 AAAGTTCTATCATCCTCTTTTCGCCCCTTTTTTCCAGCAGATAATATTAA Wajority 10660 10670 10680 10690 10700 10644 AAAGTTCTATCATCCTCTTTTGGCGCCCTTTTTCCAGCAGATAATATTAA 2603_ai1.seq 10417 AAAGTTCTATCATCCTCTTTTGGCGCCCTTTTTTCCAGCAGATAATATTAA 18rs21_ai1.seq 10649 AAAGTTCTATCATCCTCTTTTGGCGCGCCTTTTTCCAGCAGATAATATTAA cohi_ail.seq 10649 AAAGTTCTATCATCCTCTTTTGGCCCCTTTTTTCCAGCAGATAATATTAA cjbiii_aii.seq 10651 AAAGTTCTATCATCCTCTTTTGGCCCCTTTTTTCCAGCAGATAATATTAA nem316_ail.seq 10650 AAAGTTCTATCATCCTCTTTTGGCGCGCTTTTTCCAGCAGATAATATTAA a909_aii.seq GGTAGCTTGGTCTAACAACTCCAGCAGTTTATTTACACCACCTATTAATG Majority 10720 10730 10740 0694 G G T A G C T T G G T C T A A C A A C T C C A G C A C T T T A T T T A C A C C A C C T A T T A A T G 2603_ail.seq O467 GGTAGCTTGGTCTAACAACTCCAGCACTTTATTTACACCACCTATTAATC 18rs21_ail.seq 0699 GGTAGCTTGGTCTAACAACTCCAGCACTTTATTTACACCACCTATTAATG cohlail.seq GGTAGCTTGGTCTAACAACTCCAGCACTTTATTTACACCACCTATTAATG cjb111_ail.seq 0699 0701 G G T A G C T T G G T C T A A C A A C T C C A G C A C T T T A T T T A C A C C A C C T A T T A A T G nem316_ail.seq 0700 G G T A G C T T G G T C T A A C A A C T C C A G C A C T T T A T T T A C A C C A C C T A T T A A T G a909_ail.seq CAAACTACACCACTCACATTCAACCTATTCGCCACAACCATTAAAGTCACAA 10760 10770 10780 10790 0744 CAAACTACACCACTCAGATTCAAGCTATTGGGGACAACGATTAAGTCACAA 2603_all.seq 0517 CAAACTACACCACTCACATTCAAGCTATTCCACACCATTAAGTCACAAGGATTAAGTCACAAAGAAASS21_att.seq 0749 CAAACTACACCACTCACATTCAACCTATTGCGACAACGATTAAGTCACAACGII.seq 0749 CAAACTACACCACTCACATTCAACCTATTCCACACAACCATTAACTCACAACIbiil ail seq 0751 CAAACTACACCACTCACATTCAACCTATTCGGGGACAAGCATTAACTCAACAA nem316_aii.seq 0750 CAAACTACACCAGTCAGATTCAACCTATTCGCGAGAACCATTAAGICACAA a909 all seq ATTCCCCCAATTTCACCCTTACCCATAAAAAGCCCAGCAACTTCAC Najority 10810 10820 . 10830 10840 . . 10850 0794 ATT CCGGAATCGATTTTGACGGTTACGGATAAAAAGGCAGGAAGTTCAG 2603_all.seq 0567 ATTCCGGAATCGATTTTGACGGTTACGGATAAAAGAGCAGGAAGTTCAG 18rs21_a11.seq 0799 ATTCCCGAATCGATTTTGACGGTTACGGATAAAAAGAGCAGGAAGTTCAG cohl_all.seq 0799 ATTCCGGAATCGATTTTGACGGTTACGGATAAAAAGAGCAGGAAGTTCAC cjbiii aii.seq
0801 ATTCCGGAATCGATTTTGACGATTACCGATAAAAAGAGCAGGAAGTTCAG nem316 aii.seq

0800 ATTCCCGAATCGATTTTGACGGTTACGGATAAAAGAGCAGGAAGTTCAG a909_ail.seq

Alignment Report of Al- $W0\ 2006/078318$ method with Weighted residue weight table Thursday, July 29, 2004 5:46 PM CT/US2005/027239 CATTAA CAMA CHATT CAROLO ANA COT A ANA CHA A COTTAGTAGGTGCGACCTTCA Majority 10860 10870 10880 10890 10900 10844 CATTAACAAGATTGACGAAGCTAAAGAAGCTTAGTAGTGCCGACCTTCA 2603_aii.seq 10617 CATTAACAAGATTGACGAAGCTAAAGAAGGCTTAGTAGGTGCGACCTTCA 18rs21_ai1.seq 10849 CATTAACAAGATTGACGAAGCTAAAGAAGGCTTAGTAGGTGCGACCTTCA cohl_ail.seq 10849 CATTAACAAGATTGACGAAGCTAAAGAAGGCTTAGTAGGTGCGACCTTCA cjb111_a11.seq 10851 CATTAACAAGATTGACGAAGCTAAAGAAGGCTTAGTAGGTGCGACCTTCA nem316_ai1.seq 10850 CATTAACAAGATTGACGA'AGCTAAAGAAGGCTTAGTAGGTGCGACCTTCA a909_ail.seq C C T T G T C T A A A C G C A C A A C A G T A G C G G C A G A T C A T C A A G T A C A A G G A G A T Majority 10910 10920 10930 10940 10950 10894 CCTTGTCTAAACGCACAACAGTAGCGGCAGATCATCAAGTACAAGGACAT 2603_all.seq 10667 CCTTGTCTAAACGCACAACAGTAGCGGCAGATCATCAAGTACAAGGAAT 18rs21_ai1.seq 10899 C C T T G T C T A A A C G C A C A A C A G T A G C G G C A G A T C A T C A A G T A C A A G G A G À T 10899 CCTTGTCTAAACGCACAACAGTAGCGGCAGATCATCAAGTACAAGGAGAT cjbiii_aii.seq 10901 CCTTGTCTAAACGCACAACAGTAGCGGCAGATCATCAAGTACAAGGAGAT nem316_ai1.seq 10900 CCTTGTCTAAACGCACAACAGTAGCGGCAGATCATCAAGTACAAGGAGAT a909_ail.seq T T C A T T C C T G T C A G C A A A G A G A C G A C A G T C G G T C G G A C A A C C C T T A C C T T Majority 10960 -10970 10980 10990 11000 10944 TTCATTCCTGTCAGCAAAGAGACGACAGTCGGTCGGACAACCCTTACCTT 2603_all.seq 10717 TTCATTCCTGTCAGCAAAGAGACGACAGTCGGTCGGACAACCCTTACCTT 18rs21_ai1.seq 10949 TTCATTCCTGTCAGCAAAGAGACGACAGTCGGTCGGACAACCCTTACCTT cohl_ai1.seq 10949 TTCATTCCTGTCAGCAAAGAGACGACAGTCGGTCGGACAACTCTTACCTT cjbiii_aif.seq. TTCATTCCTGTCAGCAAAGAGACGACAGTCGGTCGGACAACCCTT nem316_ai1.seq .0950 TTCATTCCTGTCAGCAAAGAGACGACAGTCGGTCGGACAACTCTTACCTT a909_ai1.seq T G A C A A C C T T A A A C C T G G A T T T T A T G A C C T T A A A G A A A G C G C C G A Majority . 11020 11030 11040 11050 0994 T G A C A A C C T T A A A C C T G G A T T T T A T G A C C T T A A A G A A A C G A A A G C G C C G A , 2603_ail_seq O767 T. G. A. C. C. T. A. A. A. C. C. T. G. G. A. T. T. T. A. T. G. A. C. C. T. T. A. A. G. A. A. G. C. G. C. G. A. 18rs21_a11.seq 6999 T G A C A A C C T T A A A C C T G G A T T T T A T G A C C T T A A A G A A A C G A A A G C G C C G A cohi_all.seq D999 T G A C A A C C T T A A A C C T G G A T T T T A T G A C C T T A A A G A A A C G A A G C G C C G A cjbii1_ai1.seq
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11110 11120 11130 11140 11150 1094 G G A A A A A C G A C A A T T G T G G A T G A A G C T A A C T T C A A A G A G C C T G A T T A C C C 2603_a11.seq B67 G G A A A A A C G A C A A T T G T G G A T G A A G C T A A C T T C A A A G A G G C T G A T T A C C C 18rs21_a11, seq [099 G G A A A A A C G A C A A T T G T G G A T G A A G C T T C A A A G A G G C T G A T T A C C G cohi_ai1.seq 1099 C G A A A A A C C A C A A TT C T C G A T C A A C C T A A C T T C A A A G A G C C T G A T T A C C C c c bill all sequences of the control 100 G G A A A A C G A C A A T T C T G G A T G A A G C T A A C T T C A A A G A G G C T G A T T A C C C a909 at seq

AATGGCTGATAATACCACCCATGTGCACTGCTACCCTTGCTACAAGGAA Majority 11160 ... 11170 11180 11190 11200 144. A AT G G C T G A T A A T A C C A G C C A T C T G G A G T G C G T A G C G T T G C T A C A A C G A A 2603_a11.seq 1917 A AT G G C T G A T A A T A C C A G C C A T C T G G A G T C C G T A G C G T T G C T A C A A C G A A 18rs21-ail.seq 149 A ATGGCTGATAATACCAGCCATGTGCAGTGCGTAGCGTTGCTACAACGAA cohlail.seq 149 AATGGCTGATAATACCAGCCATGTGGAGTGCGTAGCCTTGCTACAACGAA cjbiil_ail.seq

151 AATGGCTGATAATACCAGCCATGTGGAGTGCGTAGCGTTGCTACAACGAA nem316.ai1.seq

Thursday, July 29, 2004 5:46 PM	
G C A A A G G G TA A A A T C G T T T A T T T T T A A C G A C T T T T C A A G C A T T T T C T C	r Malantes
11210 11220 11220	
11240	250
11194 G C A A A G G G T A A A A A T C C T T T A T T T T A A G C A C T T T T T C A A G C A T T T T G T C	T 2603_ail.seq
11199 G C A A A G G G T A A A A A T C C T T T A T T T T T A A G C A C T T T T T C A A G C A T T T T G T C 11201 G C A A A G G G T A A A A A T C C T T T A T T T T T A A G C A C T T T T T C A A G C A T T T T G T C	Cohi_ail.seq
11200 G C A A A G G G T A A A A A T C C T T T A T T T T A A G C A C T T T T T C A A G C A T T T T G T C	nem316_ail.seq
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T T A T T G A A A G A G T G A T T T T A A C A T A A A A A G G T A T T A A A A A C A T A T T	Majority
11260 11270 11200	300
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11244 T T A T T G A A A A G A G T G A T T T T	2603_aii.seq
11250 TTATTGAAAAGAGTGATTTTAACATAAAAAGGTATTAAAAAACATATT	a909_all.seg
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A C G T G A C C G T T T G T T T T G A A G T G G C T T G C G T A G A C A A A A A A A T A G A T A C	_ Majority
11310 11320 11330 11340 113	350 °
11294 A C G T G A C C G T T T G T T T T G A A G T G G C T T G C G T A G A C A A A A A A A A T A G A T A C C	2603 241 603
11301 A C G T G A C C G T T T G T T T T G A A G T G G C T T G C G T A G A C A A A A A A A A T A G A T A C G	nem316_all.seq
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TCAGATAAATTTCTGGCATTACGAGAACATTTTTAGAGTGTTCTCTTTT	Valority
11260 11270	-
11344 T.C.A.G.A.T.A.A.A.T.T.C.T.G.G.C.A.T.T.A.C.G.A.G.A.C.A.T.T.T.T.T.A.G.A.G.T.G.T.C.T.C.T.T.T.T.T.	2603_a11.seq
HII7 T C A G A T A A A T T T C T G G C A T T A C G A G A A C A T T T T T A G A G T G T T C T C T T T T T T T A G A G T G T T C T C T T T T T T T T T T T T	18rs21_ai1.seq
- 14070	
- 1204 - 1 0 A C A I A A A A I I I I I I I I I I I A C A C	
1350 TCAGATAAATTTCTGGCATTACGAGAACATTT TTAGAGTGTTCTCTTTTT	a909 a11.seq
T T A G T T T A C G G A G G A A A A T A T A T A T G G A A A A	_ Majority
11410 11420 11430 11440 114	
1394 TTAGTTTACGGAGGAAAATATATATGGAAAAACAGGATTCACGAGTTCT	2603 att sea
ADVILLAGILLACUGAGGAAAATATATATATATAAAAAAAAAAAAAAAAAA	40 04 44
- 4000	
1399 TTAGTTTACGGAGGAAAATATATATGGAAAAACAGGATTCACGAGTTCT	cjblli_ail.seq
1401 TTAGTTTACGGAGGAAAATATATATGGAAAAACAGGATTCACGAGTTCT	nem316_ail.seq
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CATCCATTGGGAGGGGAATTCTGGGGACAAGCTCATTGAACACCA	Valority
11460 11470 11400	•
11430 1130	JU,
1444 CATCCATTGGGAGGGGAATTCTGGGGGACAAGCTCATTGAACACCAAACCA	2603_ail.seq
1217 CATCCATTGGGAGGGGAATTCTGGGGACAAGCTCATTGAACACCAAACCA	18rs21_ai1.seq
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1450 CATCCATTGGGAGGGGAATTCTGGGGGACAAGCTCATTGAACACCAAAGCA	agog all sec
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GCGCAACGGGTGGTACTACCAAGTCGATCGTAGCTTAGTCAACCAAA	Majority.
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1494 GC GCAACG GG GT GGT ACTACCAACT CGAT CCT ACCT TA CTT ACT CAACT CGAT CGT TA CTT ACT CAACT CGAT CGT TA CTT ACT CAACT CGT TA CTT TA CTT CAACT CGT TA CTT C	maintain and the se
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1500 G C G C A A C G G G G T G G T A C T A C C A A G T C G A T C G T A G C T T A G T C A A C C A A A A	a909_a11.seq
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age 34

Thursday, July 29, 2004 5:46 PM		
GGGGAACEGECECA'GA	ATIGIAT C'GA A'AIG GE AICTAGAAAG	TGTCCGTAATGAT Majority
11560	11570 11580	11590 11600
11544 GGGGAACCGCCAGA	ATGATCCAAAGGCACTAGAAAG	
11317 G G G G A A C C G C C C A G A	ATGATCCAAAGCACTAGAAAG	TGTCCGTAATGAT 2603_a11.seq
11551 GGGGAACCGCCCAGA	ATCATCCAAACCCACTACAAAC	TGTCCGTAATGAT cjbiii_aii.seq
11550 G G G G A A C C G C C C A G A	ATGATCCAAAGGCACTAGAAAG	TGTCCGTAATGAT nem316_ai1.seq
TOURITIE GEGEGE	GATGATGTCATGGTTATGCTTA	ATAGCAAATGTAC Majority
11610	11620 11630	11640 11650
11594 T C G A T T T C G G G C G G T	GATGATGTCATGGGTTATGCTT	ATAGCAAATGTAC 2603 ail seg
11599 T C C A T T T C C C C C C C T	GATGATGTCATGGGTTATGCTTA	ATAGCAAATGTAC 18rs21_ai1.seq
11599 TCGATTTCGGGCGGT	GATGATGTCATGGGTTATGGTTA	ATAGCAAATGTAC coh1_ai1.seq
11600 TCGATTTCGGGCGGT	GATGATGTCATGGTTATGCTT	ATAGCAAATGTAC nemsio_aii.seq
11000	A C G A A T T A A T C A G T G G G A C T G A A	ACTCAAAGGTTG Majority
11660	11670 11680	11690 11700
1644 TTGGGGAGTTGCGGC	ACGAATTAATCAGTGGGACTGA	ACTCAAAGGTTG 2603 ail seg
1649 TTGGGGAGTTGCGGC	ACCAATTAATCACTCCCACTCA	ACTCAAAGGTTG cohl_all.seq
1650 TTGGGGAGTTGCGGC	A C G A A T T A A T C A G T G G G A C T G A A	A C T C A A A G G T T G a909 all seg
tizio	TACCATTACCAGTTCAATGGGAA	ATGGTCAGGATT Majority
11710	11720 11730	11740 11750
1694 AAATGGTGAGAAGAT	TACCATTACCAGTTCAATGGGAA	ATGGTCAGGATT 2603 ail.seq
	TACCATTACCAGTTCAATGGGAA	
1700 AAATGGTGAGAAGAT	TACCATTACCAGTTCAATGGGAA	ATGGTCAGGATT a909_ail.seq
	AAAGACTAGATGGTGAAACTGAT	
11760		•
	11770 11780	11790 11800
1517 G G G T T G G A A C A C C C C	A A A G A C T A G A T G G T G A A A C T G A T	ACAGTTCCAAAA 2603_ail.seq
1749 GGGTTGGAACAGCCGA	A A C A C T A C A T C C T C A A A C T C A T	A C A G T T C C A A A A 18rs21_ail.seq
1130 G G L I G G A C A C C C C G	A A G A C T A G A T G G T G A A A C T G A T	ACAGTTCCAAAA a909_a11.seq
GAAGGTACTATTCTCT	CTTTTTAGGAAAGTAGTTATGG	TTCCTATATACAX
11810		
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567 GAAGGTACTATTCTCT	CTTTTTAGGAAAGTAGTTAT.GG	TTCGTATATAGG 2603_ail.seq
	CTTTTTAGGAAAGTAGTTATGG	
SOO. G A A G G T A C T A T T C T C T	CTTTTACGAAACTAGTTATGG	TTCGTATATAGG a909_ail.seq
	TTCGTCACATTACATCTACAGA	
11860	14070	
		11890 11900
617 CTACGGAACTATATCT	TTCGTCACATTACATCTACAGA	TAGTACCATGAA 2603_all.seq
849 CTACGGAACTATATCT	TTCGTCACATTACATCTACAGA	TAGTACCATGAA 18rs21_ail.seq
SOU CTACGGAACTATATCT	TTCGTCACATTACATCTACAGA	TAGTACCATGAA a909_all.seg
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Alignment Report of Al-1_alignment, using J. Hein method with Weighted residue weight table. Thursday, July 29, 2004 5:46, P.M., ... AAAGTGAGGATATACTAACAAATGAAATAT Majority TTTTGCTTATATGACCAAGT 11910 11920 11930 11940 11894 TTTTGCTTATATGACCAAGTAAAGTGAGGATATACTAACAAATGAAATAT 2603_aii.seq 11667 TTTTGCTTATATGACCAAGTAAAGTGAGGATATACTAACAAATGAAATAT 18rs21_a11.seq TTTTGCTTATATGACCAAGTAAAGTGAGGATATACTAACAAATGAAATAT cohl_ai1.seq 11899 TTTTGCTTATATGACCAAGTAAAGTCAGGATATACTAACAAATGAAATAT cjb111_ai1.seq 11901 TTTTGCTTATATGACCAAGTAAAGTGAGGATATACTAACAAATGAAATAT nem316_ail.seq TTTTCCTTATATGACCAAGTAAAGTGAGGATATACTAACAAATGAAATAT a909_ail.seq TTATTATCGTATTTGTCCATTTTATCGAAAAGTTTGCATATTATCATTAT Majority 11960 11970 11980 11990 11944 TTATTATCGTATTTGTCCATTTTATCGAAAAGTTTGCATATTATCATTAT 2603_ai1.seq 11717 TTATTATCGTATTTGTCCATTTTATCGAAAAGTTTGCATATTATCATTAT 18rs21_ai1.seq 11949 TTATTATCGTATTTGTCCATTTTATCGAAAAGTTTGCATATTATCATTAT cohlail.seq. 11949 TTATTATCGTATTTGTCCATTTTATCGAAAGTTTGCATATTATCATTAT cjbiii_ai1.seq 11951 TTATTATCGTATTTGTCCATTTTATCGAAAGTTTGCATATTATCATTAT nem316_ail.seq 11950 TTATTATCGTATTTGTCCATTTTATCGAAAAGTTTGCATATTATCATTAT a909_ail.seq GTTTGATAAGATGCAAATATAATGATAGTAGGAGCTAAATATGGATATTT Majority 12020 12030 12050 11994 GTTTGATAAGATGCAAATATAATGATAGTAGGAGCTAAATATGGATATTT 2603_ai1.seq 11767 GTTTGATAAGATGCAAATATAATGATAGTAGGAGCTAAATATGGATATTT 18rs21_ai1.seq 11999 GTTT GATAAGATGCAAATATAATGATAGTAGGAGCTAAATATGGATATTT cohi_ail.seq. 11999 GTTTGATAAGATGCAAATATAATGATAGTAGGAGCTAAATATGGATATTT cjbii1_aii.seq 12001 GTTTGATAAGATGCAAATATAATGATAGTAGGAGCTAAATATGGATATTT nem316_a11.seq GTTTGATAAGATGCAAATATAATGATAGTAGGAGCTAAATATGGATATTT a909_ai1.seq 12000 AAAAATCAAGAGTATCCTAAGTGCTTTCCATTTTGAAATTCAAATATAG Majority 12060 12070 12080 12090 12100 12044 AAAAAATCAAGAGTATCCTAAGTGCTTTCCATTTTGAAATTCAAATATAG 2603_ail,seq 11817 AAAAAATCAAGAGTATCCTAAGTGCTTTCCATTTTGAAATTCAAATATAG 18rs21_ai1.seq 2049 AAAAATCAAGAGTATCCTAAGTGCTTTCCATTTTGAAATTCAAATATAG cohl_ail.seq 2049 AAAAAATCAAGAGTATCCTAAGTGCTTTCCATTTTGAAATTCAAATATAG cjb111_a11.seq 2050 AAAAAATCAAGAGTATCCTAAGTGCTTTCCATTTTGAAATTCAAATATAG a909_ail.seq . CTAATAGTTCTAGAACTTCTAATTCTTTTTCGTCCACGATATGAATTTTC Majority 12120 12130 12140 -2094 CTAATAGTTCTAGAACTTCTAATTGTTTTCGTCGACGATATGAATTTTC 2603_ail.seq .1867 CTAATAGTTCTAGAACTTCTAATTGTTTTTCGTCGACGATATGAATTTTC 18rs21_ai1.seq 2099 CTAATAGTTCTAGAACTTCTAATTGTTTTTCGTCGACGATATGAATTTTC cohl_ail_seq 2099 CTAATAGTTCTAGAACTTCTAATTGTTTTTCGTCGACGATATGAATTTTC cjb111_ail.seq 2101 CTAATAGTTCTAGAACTTCTAATTGTTTTTCGTCGACGATATGAATTTTC nem316_ai1.seq 2100 CTAATAGTTCTAGAACTTCTAATTGTTTTCGTCGACGATATGAATTTTC a909_ail.seq ATCTTAACTGTTAGGATTCCACCTCCCTTTGGTTAAAGAAAAAGGTCA Kajority 12160 12170 12180 12190 2144 AATCTTAACTGTTACGATTCCACCTCCCTTTGGTTAAAGAAAAAGGTCA 2603_ail.seq 1917 AATCTTAACTGTTAGGATTCCACCTCCCTTTGGTTAAAGAAAAAGGTCA 18rs21_ai1.seq 2149 AATCTTAACTGTTAGGATTCCACCTCCCTTTGGTTAAAGAAAAAGGTCA cohl_ai1.seq 2149 AATCTTAACTGTTAGGATTCCACCTCCCTTTGGTTAAAGAAAAGGTCA cjbiil all seq 2151 AATCTTAACTGTTAGATTCCACCTCCCTTTGGTTAAAGAAAAAGGTCA ném3i6 ail seq 2150 AATCTTAACTGTTAGGATTCCACCTCCCTTTCGTTAAAGAAAAAGGTCA a909_a11.seq GGTCGTTTAGATAACTTTGTCAAACAAGCTCAAGCTATCTAAAAATAGTT Majority 12210 12220 12230 .12240 12250 2194 GGTCGTTTAGATAACTTTGTCAAACAAGCTCAAGCTATCTAAAAATAGTT 2603_aii.seq 2199 G'GTCGTTTAGATAACTTTGTCAAAGCTCAAGCTATCTAAAAAATAGTT cohl_ail.seq 2199 GGTCGTTTAGATAACTTTGTCAAACAAGCTCAAGCTATCTAAAAATAGTT cjbii1_ai1.seq 2201 G G T C G T T T A G A T A A C T T T G T C A A A C A A G C T C A A G C T A T C T A A A A A A G T T nem316_a11.seq 2200 GGTCGTTTAGATAACTTTGTCAAACAAGCTCAAGCTATCTAAAAAATAGTT a909_ai1.seq

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Thursday, July 29, 2004 5:46 PM TGAAATCGCCATTACTCTTTTTTTACTACCACAACCMajority 12260 12290 12300 12244 TGAAATGGGCATTACTCTAGTTTTTAATAAGCTATCTGATGAGCAGAAGG 2603_ai1.seq 12017 T G A A A T G G G C A T T A C T C T A G T T T T T A A T A A G C T A T C T G A T G A G C A G A A G G 18rs21_a11.seq 12249 TGAAATG GGCATTACTCTAGTTTTTAATAAGCTATCTGATGAGCAAAGG coh1_ail.seq 12249 TGAAATGGGCATTACTCTAGTTTTTAATAAGCTATCTGATGAGCAGAAGG cjb111_ai1.seq 12251 TGAAATGGGCATTACTCTAGTTTTTAATAAGCTATCTGATGAGCAGAAGG nem316_ai1.seq 12250 TGAAATGGGCATTACTCTAGTTTTTAATAAGCTATCTGATGAGCAAGG a909_a11.seq AGAAGTTAATGCATGTTGGGAAGTCTTATTTTGACTATCAAGAAATGCT Majority 12310 12320 12330 12340 12350 12294 A G A A G T T A A T G C A T G T T G G G A A G T C T T A T T T T G A C T A T C A A G A A A T G C T 2603_ai1.seq 12067 AGAAGTTAATGCATGTTGGGAAGTCTTATTTTGACTATCAAGAAATGCT 18rs21_ail.seq 12299 AGAAGTTAATGCATGTTGGGAAGTCTTATTTGACTATCAAGAAATGCT cohl_ail.seq 12299 AGAAGTTAATGCATGTTGGGAAGTCTTATTTTGACTATCAAGAAATGCT cjbiii_aii.seq 12301 AGAAGTTAATGCATGTTCGGAAGTCTTATTTTGACTATCAAGAAATGCT nem316_ai1.seq 12300 AGAAGTTAATGCATGTTGGGAAGTCTTATTTTGACTATCAAGAAATGCT a909_ail.seq CTTATCCCACAATTAGGTTTTCTATATTCTAAATTAACTAAAAATTGA Majority 12360 12370 12380 12390 12400 2344 CTTATCCCACAATTAGGTTTTCTATATTCTAAATTAACTAAAAATTGA 2603_ail.seq 2117 CTTATCCCACAATTAGGTTTTCTATATTCTAAATTAACTAAAAAAATTGA 18rs21_ail.seq 2349 CTTATCCCACAATTAGGTTTTCTATATTCTAAATTAACTAAAAAATTGA cohlai1.seq 2349 CTTATCCCACAATTAGGTTTTCTATATTCTAAATTAACTAAAAATTGA cjbiil_aii.seq 2350 CTTATCCCAAATTAGGTTTTCTATATTCTAAATTAACTAAAAAATTGA 2909_ai1.seq ACTTGATAATCGGTTGTCTCCGACTGAACAAAGTTATTGATTACCTTAT Majority 12420 12430 12440 12450 2394 ACTTGATAATCGGTTGTCTCCGACTGAAAAAGTTATTGATTACCTTAT 2603_ai1.seq 2167 ACTTGATAATCGGTTGTCTCCGACTGAACAAAGTTATTGATTACCTTAT 18rs21_ai1.seq 2399 ACTTGATAATCGGTTGTCTCCGACTGAACAAAGTTATTGATTACCTTAT cohl_ail.seq 2399 ACTTGATAATCGGTTGTCTCCGACTGAACAAAGTTATTGATTACCTTAT cjb111_ai1.seq 2401 ACTTGATAATCGGTTGTCTCCGACTGAACAAAGTTATTGATTACCTTAT nem316_ai1.seq 2400 ACTTGATAATCGGTTGTCTCCGACTGAACAAAGTTATTGATTACCTTAT a909_ail.seq 12460 12480 12490 12500 2217 TATTAČATACTAAAGGTTTAATCATTGATATGTAAGAAGTAAGTCAGCTA 18rs21_ai1.seq ACCGATCTTTCTATATAAACTTATATTGTTGCTTTAGAAATTTTAAAG Majority 12510 12520 12530 12540 12550 2494 ACCGATCTTTCTAAAACTTATTGTTGCTTAGAATTTTTAAAG 2603_ail.seq 2267 A C.C.G. A T C T T T C T A T T C.T. A A A A C T T A T A T T G T T G C T T T A G A A A T T T T A A A G 18rs21_a11.seq 2499 ACCGATCTTTCTAATCTAAACTTTATTGTTGCTTAGAAATTTTAAAG cohlail.seq. 2499 ACCGATCTTTCTATTCTAAACTTATATTGTTGCTTTAGAAATTTTAAAG cjb111_a11.seq 2501 ACC.GATCTTTCTATTCTAAAACTTATTGTTGCTTTAGAAATTTTAAAG nem316_ai1.seq 2500 ACCGATCTTTCTATATATATATTGTTGCTTACTAGAAATTTTAAAG a909 all.seq AGCGTGGATGGCTTCATAATAAACAGAATCTTACCAATTTGCGAAGCCA Majority 12560 12570 12580 12590 12600 2544 A G C G T G G A T G C C T T C A T A A T A A A C A G A A A T C T T A C C A A T T T G C G A A G C C A 2603_ail.seq 2317 AGCGTGGATGGCTTCATAATAAACAGAAATCTTACCAATTTGCGAAGCCA 18rs21_ai1.seq 2549 AGCGTGGATGGCTTCATAATAAACAGAAATCTTACCAATTTGCGAAGCCA coht_all.seq 2549 AGCGTGGATGGCTTCATAATAAACAGAAATCTTACCAATTTGCGAAGCCA cjb111_ai1.seq 2551 ACCGTGGATGGCTTCATAATAAACAGAAATCTTACCAATTTGCGAAGCCA nem316_ai1.seq 2550 A G C G T G G A T G G C T T C A T A A T A A A C A G A A A T C T T A C C A A T T T G C G A A G C C A a909_ai1: seq

hursday, July 29, 2004 5:46 PM AAAAATAFFGATATTTTGAAAGATAGTTTAG Wajority 12610 12630 12640 12650 2600 AAAAAATATGATATTGAAGAGTCCAAAGATCTAATAGATACTCCACTTAG a909_aii.seq A G A A G C C T T G A T T A T A A C T G A T A A G G A T T T T C A A A A A T T A A A A C A A G A G C Majority 12660 12670 12680 12690 12700 2651 AGAAGCGTTGATTATAAGTGATAAGGATTTTCAAAAATTAAAACAAGAGC nem316_at1.seq TATTATTTTAACCGACTTATTTTAAAGACTTATCATATCTAGCCTTGCTT Majority 12710 12730 12740 12750 GATGATTCGGAAAAATACGGAGACTATACTATTTCAAGGAAAAGATACAA Majority 12760 12770 12780 12790 12800 2744 GATGATTCGGAAAAATACGGAAGATACTATTCAAGGAAAAGATACAA 2603_ai1.seq 2517 GATGATTCGGAAAAATACGGAGACTATACTATTTCAAGGAAAAGATACAA 18rs21_ai1.seq 2749 GATGATTCGGAAAAATACGGAGACTATACTATTTCAAGGAAAAGATAC.AA cohlait.seq 2749 GATGATTCGGAAAAATACGGAGACTATACTATTTCAAGGAAAAGATACAA cjb111_a11.seq 2750 GATGATTCGGAAAAATACGGAGACTATACTATTTCAAGGAAAAGATACAA a909_a11.seq AAGTTTCGAATCAAGTCTTCAACTATACATCCTTCAAAGTCATCGCTAG Majority 12810 12830 12840 2794 AAGTTTCGAATCAAGTCTTCAACTATACATCCTTCAAAGTCATCGCCTAG 2603_a11.seq 2567 AAGTTTCGAATCAAGTCTTCAACTATACATCCTTCAAAGTCATCGGCTAG 18rs21_a11.seq 2799 A A G T T T C G A A T C A A G T C T T C A A C T A T A C A T C C T T C A A G T C A T C G G C T A G cohl_ail.seq 2799 AAGTTTCGAATCAAGTCTTCAACTATACATCCTTCAAAGTCATCGGCTAG cjb111_ai1.seq 2801 A A GTTTCGAATCAAGTCTTCAACTATACATCCTTCAAAGTCATCGGCTAG nem316_all.seq 2800 A A G T T T C G A A T C A A G T C T T C A A C T A T A C A T C C T T C A A G T C A T C G G C T A G a909_a11.seq A G A T T T G G A A T T A T G A A C C A A T C C C T T T G A T T A C T A G A A A A A A A A A G C Majority 12860 12870 12880 12890 12900 2844 A G A T T T G G A A T T A T G A A C C A A T C C C T T T G A T T A C T A G A A A A A T A A A T A G C 2603_ai1.seq.
2617 A G A T T T G G A A T T A T G A A C C A A T C C C T T G A T T A C T A G A A A A A A A A A A A A A A A G C 18rs21_ai1.seq 2849 A G A T T T G G A A T T A T G A A C C A A T C C C T T T G A T T A C T A G A A A A A A A A A A G C cohl_all_seq 2849 A G A T T T G G A A T T A T G A A C C A A T C C C T T T G A T T A C T A G A A A A A T A A A T A G C cjbiii aii. seq 2851 A G A T T T G G A A T T A T G A A C C A A T C C C T T T G A T T A C T A G A A A A A T A A A T A G C nem316 aii. seq TTGGAGAGGCTAACGTGACACTGGTTGATCCAATCTCGCTTTATTAACA Wajority 12910 12920 12930 12940 12950 399 TT G G A G A G G C T A A C G T G A C A C T G G T T G A T C C A A T C T C G C T T A T T T A A C A cjbiii_aii.seq 901 TTGGAGGGCTAACGTGACACTGGTTGATCCAATCTCGCTTTATTAACA nem316_a11.seq

PCT/US2005/027239

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Alignment Report of Al-1_aiignment, using J. Hein method with Weighted residue weight table.
Thursday, July 29, 2004 5:46 PM. CTAAGAAT CATCA

A A G A A G A A G A A G T T G A G C A G C T A G A A Majority 12960 12970 12980 12990 12944 CTAAGAATGATGAAGACCCTCGTATTGAAGAAGTTGAGCAGCTAGAA 2603_ai1.seq
12717 CTAAGAATGATGAAGACCCTCGTATTGAAGAAGATTGAGCAGCTAGAA 18rs21_ai1.seq 12949 CTAAGAATGAAGACCCTCGTATTGAAGAAGTTGAGCAGCTAGAA cohl_all.seq 12949 CTAAGAATGATGAAGACCCTCGTATTGAAGAAGTTGAGCAGCTAGAA Cjb111_ai1.seq
12951 CTAAGAATGATGAAGACCCTCGTATTGAAGAAGTTGAGCAGCTAGAA cjb111_ai1.seq 12950 CTAAGAATGATGAAGACCCTCGTATTGAAGAAGTTGAGCAGCTAGAA a909_ai1.seq

GATAAGAT

12994 GATAAGAT 12767 GATAAGAT 12999 GATAAGAT 12999 G A 13000 A

I3000 GATAAGAT

Majority

2603_all.seq 18rs21_ai1.seq cohi_ail.seq cjblil_ail.seq nem316_ail.seq a909_ail.seq

Decoration 'Decoration #1': Shade (with solid black) residues that differ from the Consensus.

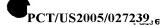
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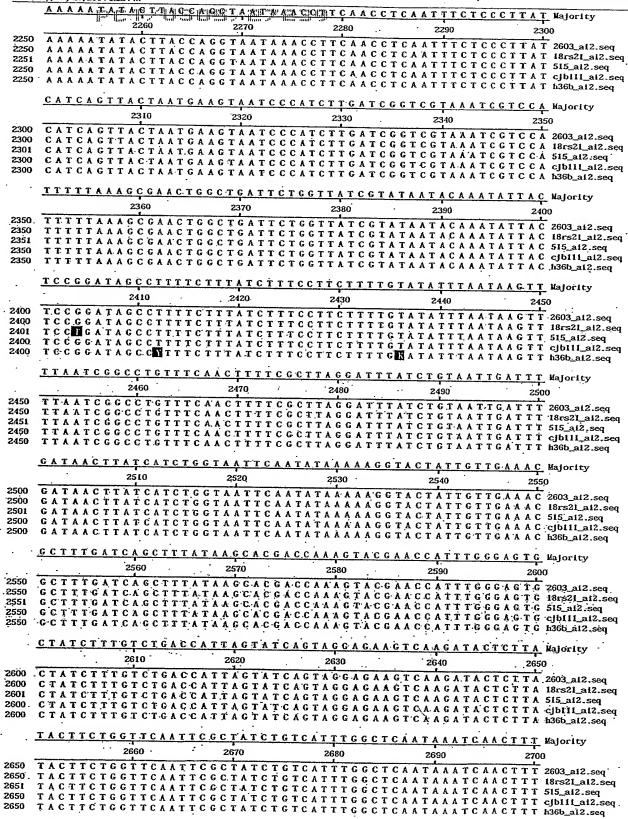
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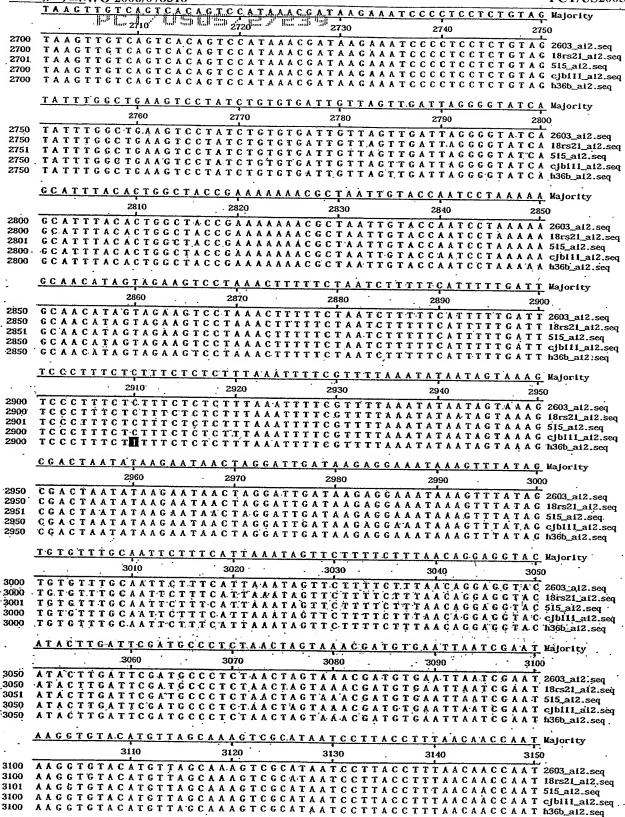
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901	TTACAGTATT	ACCAATCACAC	TGATTAA	CTTGAAAA	T C T T G T A G A A A G T C T T G T A G A A A G	A 18rs21 at2-seq
901	TTACAGTATT	ACCALTCACAC	****	O T T G A A A A A	LICILGIAGAAAG	A 515_ai2.seg
901	TTACAGTATT	ACCAATCACAC	FIGATIKA	CTTGAAAAA	TCTTGTAGAAAG TCTTGTAGAAAG	A cibili ai2.seg
		NOCKRICACA(IGAITAA	CTTGAAAAA	T C T T G T A G A A A G T C T T G T A G A A A G	A h36b_a12.seq
	TTTGGCAACT	GTCCTCTAACA		C	GGTCAAATGAAA	•
	960	2 11 11 0 11	CITICII		GGTCAAATGAAA	T Majority
		. 510		980	990 1	000
951	TTTGGCAACT	GTCCTCTAACA	CTTTCTT	GAATAGTTT	GGTCAAATGAAA	T 2000
951	TTTGGCAACT	G T C·C T C T A A C A	CTTTCTT	GAATAGTTT	G G T C A A A T G A A A G G T C A A A T G A A A	T 18-031 - 12
951 951	TTTGGCAACT	GTCCTCTAACA	CTTTCTT	GAATAGTTT	G G T C A A A T G A A A	T 515 312 500
951	TTTCCCAACT	GT C C T C T A A C A	CTTTCTT	GAATAGTTT	G G T C A A A T G T A A A G G T C A A A T G A A A	T cibili al2 con
001	IIIOGCARCI	GIC. CTCTAACA	CTTTCTT	GAATAGTTT	G G T C A A A T G A A A G G T C A A A T G A A A	T h36b al2.seg
	TACAGTGTCGG					
		SOCCARIATII	GATGACC	AATCCTAAA	CTGAAAAATAAG	A Majority
	1010	1020		1030	1040	050
1001	TACAGTGTCGC	GGCCAATATTT	CATCACC	1 1 T C C T C / 1		
1001	TACAGTGTCG	GGCCAATATTT	GATGACC	AATCCTAAA	CTGAAAAATAAG CTGAAAAATAAG	A 2603_a12.seq
1001	TACAGTGTCGG	GGCCAATATTT	GATGACC	AATCCTAAA	C T G A A A A A T A A G	A 18rs21_a12.seq
1001	TACAGTGTCGG	GGCCAATATTT	GATGACC	AATCCTAAA	CTGAAAAATAAG CTGAAAAATAAG	A 515_a12.seq
- 1001	TACAGTGTCGG	3 G C C A A T A T T T	GATGACC	AATCCTAAA	C T G A A A A A T A A G C T G A A A A A T A A G	A cjbiii_ai2.seq
		•	•		O I G K K K K K K K K K	A nob_aiz.seq
	TAATAGCAATA	AATGCTTGAA	TAAGTTI	ACTATTTTG	ACGAGATAACAT	T Valority
	1060	1070		1080		•
1051		,			1090	100
1051	TAATAGCAATA	AATGCTTGAA	TAAGTTT	ACTATTTTG	ACGAGATAACAT	T 2603 al2.seg
1051	TAATAGCAATA	AAIGCTTGAA	TAAGTTT	ACTATTTTG	A C G A G A T A A C A T	T 18rs21 a12.seg
1051	TAATAGCAATA	AAIGCIIGAA	TAAGTTT	ACTATTTTG	A C G A G A T A A C A T	T 515_ai2.seq
1051	TAATAGCAATA	AATGCTTGAA	TAAGITT	ACTATTTT	A C G A G A T A A C A T :	r cjblil_ai2.seq
		- I I I I I I I I I I I I I I I I I I I	I St N.O I I I	ACIALITIE	ACGAGATAACAT	I h36b_ai2.seq
	AGTCTTTTAT	ATCTTTCTAA	TATTEGE	AAACAAGCC	A C G T A A G T T A G A 1	
	1110	****			ACGIA.AGIIAGA	Majority
****		40		1130	1140 _ 11	50
1101.	AGTCTTTTAT	ATCTTTCTAA	TATTGGC	AAACAAGCC	ACGTAAGTTAGAT	L 2603 212 602
1101	ACTOTTTTTAT	ATCTTTCTAA	TATTCCC	A A A C A A G C C	A C G T A A G T T A G A T A C G T A A G T T A G A T	18rs21 at2 sea
1101	ACTOTITIES	ATCITTCTAL	TATTGGC	AAAGAAGCC	A C G T A A G T T A G A 1 A C G T A A G T T A G A 1	515 al2.seg
1101	AGTCTTTTTAT	ATCTTTCTAL	TATTGGC	A A A C A A G C C .	A C G T A A G T T A G A 1 A C G T A A G T T A G A 1	cjbili_ai2.seg
		RICITICIAN	PARTGGC	AAACAAGCC.	A C G T A A G T T A G A 7 A C G T A A G T T A G A 7	h36b_a12.seq
	AGAAAACAATC	GAAATTAAÀA	Ттесете:	A A C C A T A T T	A A T G G A A T A A C C	•
	1100				<u> </u>	_ Kajority
	1160	1170		1180	1190 120	
1151	AGAAAACAATC	GAAATTAAAA	TTCCCTC	AACGATATT	AAATGGAATAACC	2000 - 10
1151						
1151	AGAAACAATC	GAAATTAAAA	FTCCCTC	AACGATATT	A A T G G A A T A A C C A A A T G G A A T A A C C	515 at2 sea
1151 1151	ACAAAACAATC	GAAATTAAAA	TTC.CCTC.	A A Ċ G A T A T Ť A	A A T G G A A T A A C C	cibili ai2 sea
1131		GAAATTAAAA.	TTCCCTC	A C G A T A T T I	A A T G G A A T A A C C A A T G G A A T A A C C	h36b ai2.seg
	ATTGTTAAAAAC	CT A A TT C C C m				
	ZZZZZZZZZZZZZZZZZZZZZZZZZZZZZZZZZZZZZZ	GIARIIGC CIA	CACCAAI	AAATGTTC1	GATATCAAAGTT	Majority .
_		· 1220	•	1230	1240 126	:n ·
1201	ATTGTTAAAAG	GTAATTGCCT	CACCAA.	CAAATCTTCT	1	•
1201	ATTGTTAAAAG	GTAATTGCCT	CACCAAT		GATATCAAAGTT GATATCAAAGTT	18rs21_a12.seq
1201	ATTGTTAAAAG	GTAATTGCCT	CACCAAT	CAAATGTTCT	GATATCAAAGTT GATATCAAAGTT	515_a12.seq
1201	ATTGTTAAAAG	GTAATTGCCTA	CACCAAT	AAATGTTCT	GATATCAAAGTT GATATCAAAGTT	cjbiii_aiz.seq
					SA FRI DANK GIT	nson_aiz.seq
•	AGCAAATATAG	C A'T A C A A A G G A	ATCGCA'A	AGACATAGT	TGAGAGCTACCA	Valority
٠.	1260	1270		1280		
1251					1290 130	0
1251	ACCALATATAC	CATACAAAGGA	ATCGCAA	AGACATAGT	T G A G A G C T A C C.A	2603 al2.seg
1251	AGCAAATATAG	CATACAAAGGA	ATCGCAA	AGACATAGT	TGAGAGCTACCA	515_ai2.seq
		·	WICEC W.V	AGACATAGT	TGAGAGCTACCA TGAGAGCTACCA	h36b_a12.seq
					TTAATAAAATCT	
•	1010		O O A A A, F	TORUTAGET	I I A A I A A A A T C T	Kajority
	. 1310	1320	. 1	1330	1340 1350	0 .
1301	TAGATACGGTCA	AAGCTAACTGT	ACCAAAT	AGACTACCT		
1301	TAGATACGGTCA	AAGCTAACTGT	ACCAAAT	AGACTACCT	TTAATAAAATCT	2003_a12.seq
1301	TAGATACMGTCA	AGCTAACTGT	ACCAAAT	AGACTAGCT	TTAATAAAATCT	sis all co-
1301	A G A T A C G G T C A	AGCTAACTGT	ACCAAAT	AGACTAGCT	TTAATAAAATCT TTAATAAAAATCT	cibili ai2 sos
1301	PAGATACGGTCA	LAGCTAACTGT	ACCAAAT	AGACTAGCT	TTAATAAAATCT	h36b al2-seg
		•	•			
			•			

- Trui	suay, July 29, 2 W O 2000/0 / 8318	FC1/US2003
	TTTGCACTCTCTATTTTTCCAGAAAATAGCGAAACTTGCTAAAAT	A Motorten
	I'' Ilou 1960 'and 'and and therefore it has sail all the	K Kajority
170	1370 1380 1390	1400
135 135		A A 2603 312 500
135	I TTTGCACTCTCTCTATTTTTCCAGAAATAGCGAAACTTGCTAAAAAT	A A 18rs21 at2 seg
135	TTTGCACTCTCTATTTTCCAGAAATAGCGAAACTTGCTAAAAAT	A A 515 ai2 seg
1351	TTTGCACTCTCTCTATTTTCCAGAAAATAGCGAAACTTGCTAAAAAT	A A cibili al2 seg
100.	TTTGCACTCTCTATTTTTCCAGAAATAGCGAAACTTGCTAAAAAT	A A h36b_a12.seg
	AGCTAGAGCAACCATATTCATCCCTAAACCAA	•
	ACCTAGAGCAACCATATTCATCGGTAAACCAATAAACGTTTCTGGACCA	A C Majority
	1410 1420 1430 1440	1450
1401		
1401		
1401	AGCTAGAGCAACCATATTCATCGGTAAACCHATAAACGTTTCTGGACCA	A C 18rs21_a12.seq
1401		
1401	A G C T A G A G C A A C C A T A T T C A T C G G T A A A C C A A T A A A C G T T T C T G G A C C A	A C CONTINUE AIZ. Seq
	GATTAGCAAGTATAACTTTTAAAAGTGATCTTAATAAGAGTACACCATA	A Majority
	1460 1470 1400	•
1451	1.30	1500
1451		A A 2603_a12.seg
1451		
	GATTAGCAAGTATAACTTTTAAAAGTGATCTTAATAAGAGTACACCATA	\ A 515_a12.seq
1451	GATTAGCAAGTATAACTTTTAAAAGTGATCTTAATAAGAGTACACCATA	l A cjblli_al2.seq
	THE THE TAX A G I GAT C I LAAFA G A G T A C A C C A T A	A h36b_ai2.seq
	CTT CATTT CAAATCAAATAAAATAAAAG CAACTAACAT C G G AA G G ATT G	
		A Majority
	1510 1520 1530 1540	1550
1501	CTT GATTT CAAAT CAAATAAAATAAAA G CAACTAA CAT CG GAA G GATT G	14.0000
. 1501	CTT G A T T C A A A T C A A A T A A A A A G C A A C T A A C A T C G G A A G G A T T G	A b36b at2 sea
	AAAAT CAACCTTTAAAAATTCTGCTCCTGGTATTAATGGAAATGAAACC	A Majority
•	1560 1570 1570	1600
1551		- L .
1551	AAAAT CAACCTTTAAAAATTCTGCTCCTGGTATTAATGGAAATGAAACCAAAAAATTCTGCTCCTGGTATTAATGGAAATGAAACC	
1551	AAAATCAACCTTTAAAAATTCTGCTCCTGGTATTAATGGAAATGAAACC	A 18rs21_a12:seq
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1551	A A A T C A A C C T T T A A A A T T C T G C T C C T G G T A T T A A T G G A A T G A A A C C	A cjbiii_ai2.seq
	TCATCAATACAAAAGATAAGGCAGAAAGAATGGCGATTGTCACCATTTT	A Majority
	1610 1620 1000	•
1601		650
1601	TCATCAATACAAAAGATAAGGCAGAAAGAATGGCGATTGTCACCATTTT	A 2603_ai2.seq
1601	T C A T C A A T A C A A A A G A T A A G G C A G A A A G A A T G G C G A T T G T C A C C A T T T T T T C A T C A A T A C A A A A	A cjblll_a12.seq
	CCT GT A T T T G T C A T A A A A A A T T C C T C C A A T T T A A T A A A T T G A A A G A A	A 44
•		G Majority
	1000 1090	700
1651	CGTGTATTTGTCATAAAAAAATTCCTCCAATTTAAATAAA	C 2603 312 sea
1031	C G T G T A T T T G T C A T A A A A A A A T T C C T C C A A T T T A A A T A A T T G A A A G A A	G h36b al2.seg
	CTCCAAAGGTAAGCGTATGTACGCGAAAAAA.CCTTTGTCTCTCCCAT	C Majority
• ;	1710 1720	750
1701 -		730 . J.,
1701	CTCCAAAGGTAAGCGTATGTACGCGAAAAAA - CCTTTGTCTCTCCCAT.	C 2603_a12.seq
1701	CTCCAAAGGTAAGCGTAMGTACGCCAAAAAAACCCTTTGTCTTCTCCCAT	C 18rs21_a12.seq
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	CTCCAAAGGTAAGCGTATGTACGCGAAAAAA-CCTTTGTCTTCTCCCAT	
	CAGACTTTACTGTCGGTTGTGGAATCTCACCACATCAGCTTTCGCTCGC	
		u Hajority
	1760 1770 1780 1790 18	300
1750	CAGACTTTACTGTCGGTTGTGGAATCTCACCATCACCTTTTGGGTTGTG	<u>. </u>
1750	CAGACTTT A CTGTCGGTTGTGGAATCTCACCACATCAGCTTTCGCTCGC	C 6365 a12 a
	·	, woo_ara.seq

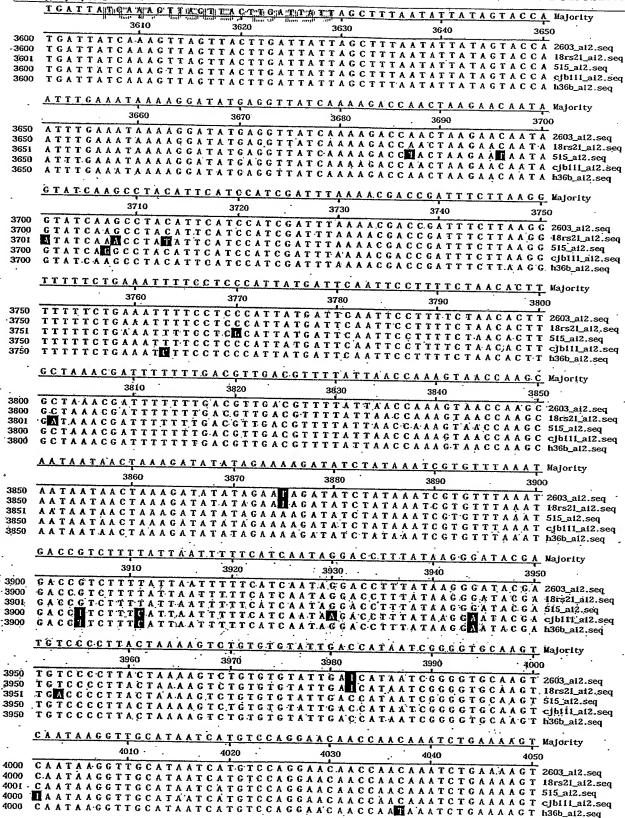
GACTGATGCTTCACAACTGACAAATAAGTTGGAAGCGATTACCGCCGGTC Majority
1830 1840 1850 GACTGATGCTTCACAACTGACAAATAAGTTGGAAGCGATTACCGCCGGTC 2603_al2.seq 1800 GACTGATGCTTCACAACTGACAAATAAGTTGGAAGCGATTACCGCCGGTC 18rs21_a12.seq GACTGATGCTTCACAACTGACAAATAAGTTGGAAGCGATTACCGCCGGTC 515_a12.seq 1801 GACTGATGCTTCACAACTGACAAATAAGTTGGAAGCGATTACCGCCGGTC cjbiiLai2.seq 1800 GACTGATGCTTCACAACTGACAAATAAGTTGGAAGCGATTACCGCCGGTC h36b_at2.seq 1800 G G G A A T T A C A C C C T G C C C T G A A G A C C C T A T A G C A T A A C A A A A A A A C T T Najority 1860 1870 1880 1890 G G G A A T T A C A C C C T G C C C T G A A G A C A C C T A T A G C A T A A C A A A A A A A C T T 2603_at2.seq 1850 G G G A A T T A C A C C C T G C C C T G A A G A C A C C T A T A G C A T A A C A A A A A A A A C T T 18rs21_a12.seq 1850 1851 1850 GGGAATTACACCCTGCCCTGAAGACACCTATAGCATAACAAAAAAACTT h36b_a12.seq 1850 1920 1930 1940 1950 GCAATTGCAAGTTTTTTAATTACTAATTAGTAGTAGTAGTTAAAAAATCAT 2603_a12.seq 1900 GCAATTGCAAGTTTTTTAATTACTAATTAGTAGTAGTAGTAAATTAAATCAT 18rs21_a12.seq 1900 GCAATTGCAAGTTTTTTAATTACTAATTAGTAGTAGTAATTAAAAATCAT 515_a12.seq 1901 GCAATTGCAAGTTTTTTAATTACTAATTAGTAGTAGTGATTAAAAATCAT cjbiil_ai2.seq .1900 GCAATT-GCAAGTTTTTTAATTACTAATTAGTAGTAGTGATTAAAAAATCAT h36b_ai2.seq 1900 ATT.AATACCAAATTACTATACTGTATCGTTTCTTTCAGATTTGCTATTTT Majority . 1970 . 1980 1990 ATT AATACCAAATTACTATACTGTATCGTTTCTTTCAGATTTGCTATTTT 2603_al2.seq 2000 1950 ATTAATACCAAATTACTATACTGTATCGTTTCTTTCAGATTTGCTATTTT 18rs21_ai2.seq -1950 ATTAATACCAAATTACTATACTGTATCGTTTCTTTCAGATTTGCTATTTT 515_ai2.seq 1951 ATTAATACCAAATTACTATACTGTATCGTTTCTTTCAGATTTGCTATTTT cJb111_a12.seq ATTAATACCAAATTACTATACTGTATCGTTTCTTCAGATTTGCTATTTT h36b_al2.seq 1950 TAGTTTTTCTTAAAAAGATAAACAAATTCCCAAAATAATACAACCAAGA Majority 2010 2020 2030 2040 2050 TAGTTTTTCTTAAAAAGATAAACAAAATTCCCAAAATAATACAACCAAGA 2603_a12.seq 2000 TAGTTTTTCTTAAAAAGATAAACAAAATTCCCAAAATAATACAACCAAGA 18rs21_a12.seq 2000 TAGTTTTTCTTAAAAAGATAACAAATTCCCAAAATAATACAACCAAGA 515_a12.seq 2001 TAGTTTTCTTAAAAAGATAAAAAATTCCCAAAATAATACAACCAAGA cjbiiLai2.seq 2000 TAGTTTTCTTAAAAAGATAAACAAATTCCCAAAATAATACAACCAAGA h36b_al2.seq 2000 ATTGTCAGTCCTC.CACCAATAATCATTCCTGTTTTAGGAAGAAATGATTG Majority 2060 2070 2080 2090 2100 ATTGTCAGTCCTCCACCAATAATCATTCCTGTTTTAGGAAGAATGATTG 2603_al2.seq 2050 ATTGTCAGTCCTCCACCAATAATCATTCCTGTTTTAGGAAGAATGATTG 18rs21_ai2.seq 2050 ATTGTCAGTCCTCCACCAATAATCATTCCTGTTTTAGGAAGAAATGATTG 515_ai2.seq 2051 ATT GT CAGT CCT CCACCAATAAT CATT CCT GT TT TAGGAAGAAAT GATT.G cjbiil ai2.seq 2050 ATTCTCAGTCCTCCHCCAATAATCATTCCTGTTTTAGGAAGAAATGATTG h36b_ai2.seq 2050 TGGAAAAGCGGTTGTGATGGTTTAGGATTTGTTGGTGGAGGAGTTTCTT Majority 2110 2130 2140 2150 2100 TG GAAAAA GC GGTTGTGATGGTTTAGGATTGTTGGTGGAGGAGTTTCTT 2603_ai2.seq 2100 TGGAAAAACCGGTTGTGATCGTTTAGGATTTTTTTTGGTGGAGGAGTTTCTT 18rs21_ai2.seq TOGAAAAAGCGGTTGTGATGGTTTAGGATTTGTTGGTGGAGGAGTTTCTT. 515_ai2.seq TGGAAAAAGCGGTTGTGATGGTTTAGGATTTGTTGGTGGAGGAGTTTCTT cjb111_at2.seq 2100 TTTCGTTTCTACCTCTACTTCCTGTGTTTTATTAGCAACTACAGCAACT 2160 2180 :2170 2190 2200 TTTCGTTTTCTACCTCTACTTCCTGTGTTTTATTAGCAACTACAGCAACT 2603_at2.seq . 2150 TTTCGTTTTCTACCTCTACTTCCTGTGTTTTATTAGCAACTACAGCAACT 18rs21_a12.seq .2150 2151 TTTCGTTTTCTACCTCTACTTCCTGTGTTTTATTAGCAACTACAGCAACT cjbiil_ai2.seq 2150 TTT CGTTTTCTACCTCTACTTCCTGTGTTTTATTAGCAACTACAGCAACT h36b_a12,seq - 2150 ACAGCATCCTTCATAGATATACGGTAACCAGTTAGTGCTTTTGCTTCTCG Wajority 2210 2220 2230 2240 ACAGCATCCTTCATAGATATACGGTAACCAGTTAGTGCTTTTGCTTCTCG.2603_a12.seq 2250 2200 ACAGCATCCTTCATAGATATACGGTAACCAGTTAGTGCTTTTGCTTCTCG 18rs21_a12.seq 2200 ACAGCATCCTTCATAGATATACGGTAACCAGTTAGTGCTTTTACTTCTCG 515_a12.seq 2201 ACAGCATCCTTCATAGATATACGGTAACCAGTTAGTGCTTTTGCTTCTCG cjbiii_ai2.seq 2200 ACAGCATCCTTCATAGATATACGGTAACCAGTTAGTGCTTTTGCTTCG h36b_a12.seq

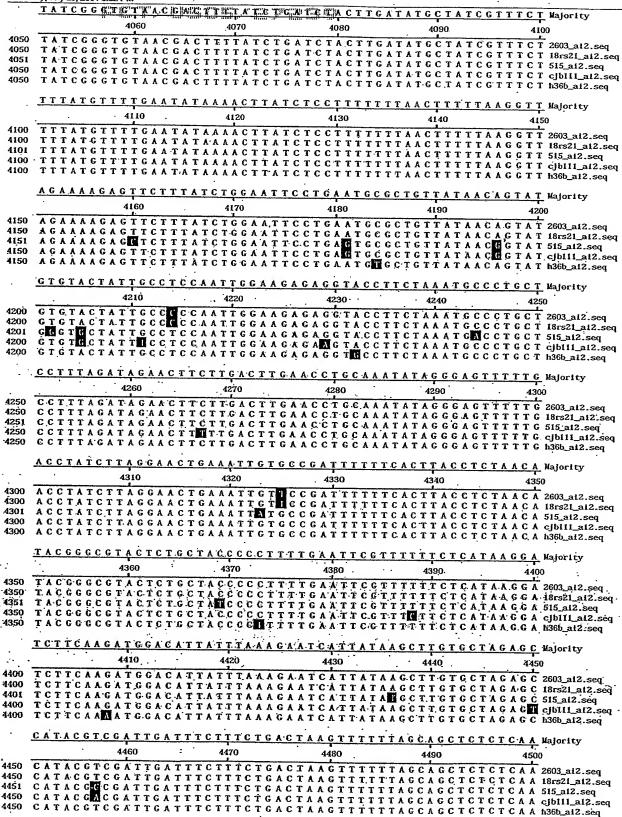


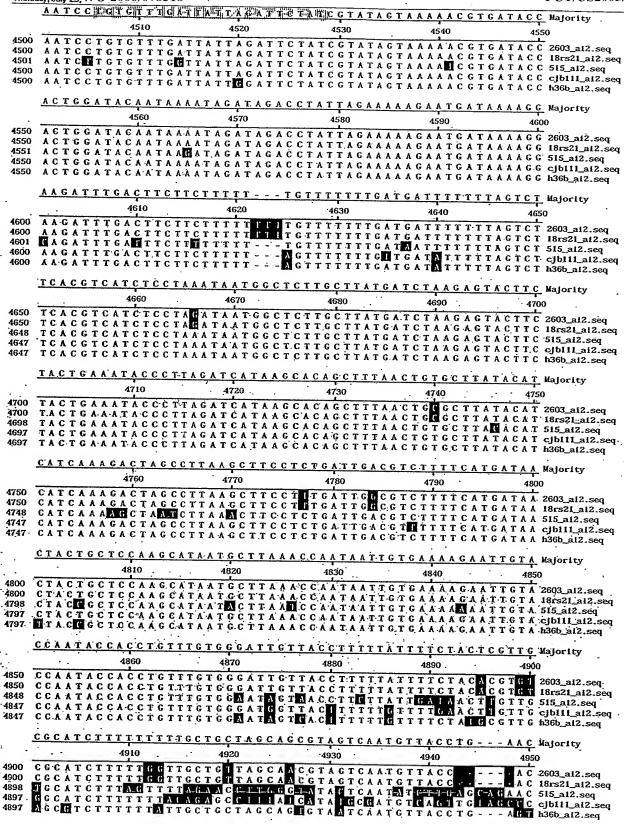


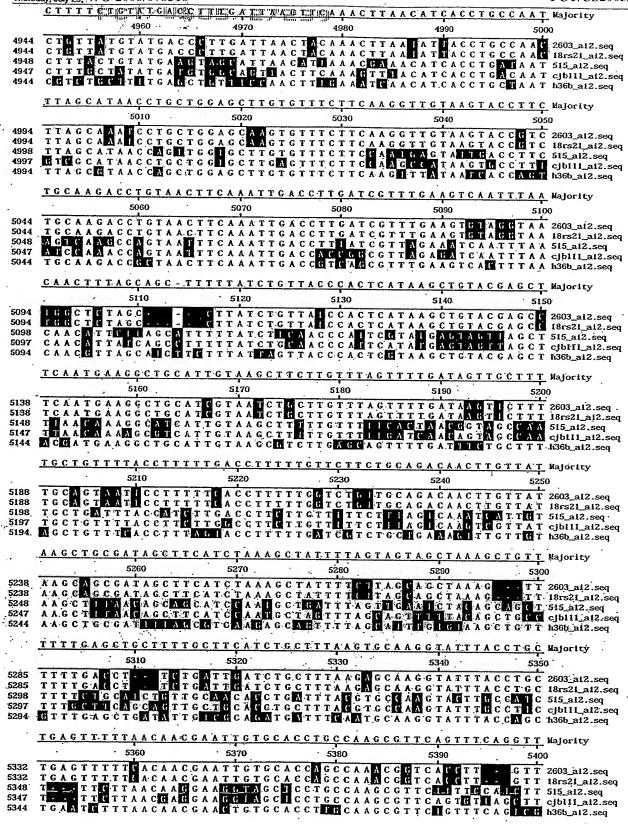


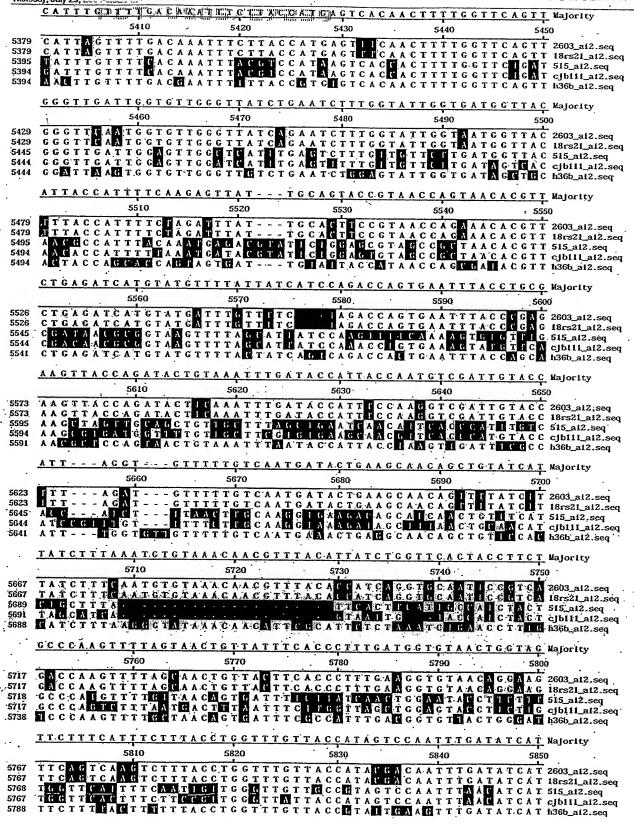
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	AATT	T A.G A.A.A.A	ATTATCTC	G.C.T.T.T.A.C.A	A.CACTTATTT	GATCAACCTTAT	F.A Majority
•		3160	3	170"""." """"	" ["] 3180	3190	3200
3150	A A.T T	TAGAAAA	ATTATCTG	GCTTTACA	ACACTTATT		
3150 3151	AATT	TAGAAAA	ATTATCTG	GCTTTACA	ACACTTATT	GATCAACCTTAT GATCAACCTTAT	I A 2603_ai2.seq
3150		I A G A A A A	ATTATCTC	GCTTTACA	ACACTTATTT	GATCAACCTTA1 GATCAACCTTA1	Γ A 515_a12.seq
3150	AATT	TAGAAAA	ATTATCTG	G C T T T A C A /	A C A C T T A T T T	G A T C A A C C T T A T G A T C A A C C T T A T G A T C A A C C T T A T	A cjbliLai2.seq
	GGCT	LAAACTT	CTTTGATA	TTATGAATA	TAAAAAATT	TTTCCTTTTTTA	A Majority
	-	3210	· 32	220	3230	3240	3250
3200	GGCT	AAACTT	CTTTGATA	TTATGAAT	TAAAAAATT	T T T C C T T T T T T T T T T T T T T T	_L
3200 3201	GGCT.	AAACTT	CTTTGATA	TTATGAATA	A.T.A.A.A.A.T.T	TTTCCTTTTTT	i A 2603_at2.seq i A 18rs21_at2.seq
3200							
3200	GGCT	AAACTT	CTTTGATA	I I A I G A A T A T T A T G A A T t	LTAAAAAAATT LTAAAAAAATT	1	A cjb111_a12.seq
					LIARRARALI		A h36b_a12.seq
	GITTA	TCTAAA	TCTGTAAA	TAACTTAGC	TTTAGGTAA	GCCGCGATGAGC	T Majority
•		3260	32	70	3280		3300
3250	GTTT	TCTAAA	TCTGTAAA	FAACTTAGC	TITAGGTAA		
3250 3251							
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3250						G C C G C G A T G A G C G C C G C G A T G A G C G C C G C G A T G A G C	
	GTGAT	AACAGT	ATGTGAACT	TTTTCCAC	CAATTGGCAA	GGAGGTTCCTT	C Majority
		3310		20	3330		3350
3300	GTGAT	AACAGT.	ATGTGAACT	TTTTCCAC	CAATTGGCA		_1_
3300 3301							
3300	GTGAT	AACAGT.	A T G T G A A C T	TTTTCCAC	CAATTGGCAA	A G A G G T T C C T T	C 515_a12.seq
3300						AM GAMGTTCCTT AGGAGGTTCCTT AM GAMGTTCCTT	
•	AAGGT	GTCCTG	CTCCTTTTT	CAAGAACA	CTACTGGTAG	TCCCCGCATAG	A Majority
		3360	33		3380		400 .
3350	AAGGT	GTCCTG	CTCCTTTT	CAAGAACA	CTACTGGTAG		
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3350						T C C C C G C A T A G T C C C C G C A T A G T C C C C G C A T A G	
	IAGGL	AATTITT	GCTTGATA	GACGGTAT.	<u>ATCAATATAT</u>	CCAATCATTTC	A Majority
		3410	342		3430	3440 3	450
3400	TAGGT	AATTTTT	r.G C T T G A T A	GACGGTAT	ATCAATATAT	CCAATCATTTC	L 2603 a12 sea
3400 3401							
3400	TAGGT	AATTTTT	CCTTCATA	CACCCTAT	AICAAIAIAI	CCAATCATTTC	A 515_a12.seq
3400	TAGGT	AATTTTT	GCTTGATA	GACGGTAT	ATCAATATAT	C C A A T C A T T T C	A cjbili_ai2.seq
	<u>GURAI</u>	CICAAGC	AIGGGC	GTATTCAG	CAATACCTTT	TTTTTCTTTTT	C_Majority
		3460	347		3480	3490 35	500
3450	GCAAT	C·T C A A G C	ATGTGGGC	GTATTCAG	CAATACCTTT	TTTTTCTTTT	ւ. C 2603 at2.sea
3451							
3450						TTTTTCTTTTT TTTTTCTTTTT	
3450	GCĄĄT	CTCAA.GC	A T.G.T.G G G C	GTATTCAG	CAATACCTT	TTTTTCTTTT	C cjblll_ai2.seq.
٠.	AGIA.I	N G G G K I L	TGALAGGE	GGCTTGGGT	<u> </u>	TATTATAAGCT	L. Majority
		3510	. 352		3530	3540 35	50
3500	AGTAT.	AGGGATC	TGATAGGC	GGCTTGGG	T C C A G T G T T C	TATTATAAGCT	L . Γ. 2603: a12. seα
3500 3501							
3500	A G T. A.T	AGGGATC	TGATAGGC	G G C T T G G G C	I C C A C T C T T C	TATTATAAGCTT	515_a12.seq
3500	AGTAT.	AGGGATG	TGATAGGC	GGCTTGGGT	CCAGTGTTC	TATATA AGCT 1 TATATA AGCT 1	Cjbiii_ai2.seq
	11661	CACICAA	ATCGTCTA	<u> FTAATCTCT</u>	TTAGTATTT	AATTTTTGGGTT	<u> Najority</u>
	·	3560	3570		3580	3590 36	00
3550	TTGCT	ACTCAA	ATCGTCTA	TTAATCTCT	TTAGTATTT	1 1 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	
3550	TTGCT	ACTCAA	ATCGTCTA		LIIA G RM ATTT. PTT 4 CT 4 TTT	AATTTTTGGGTT	515_a12.seq
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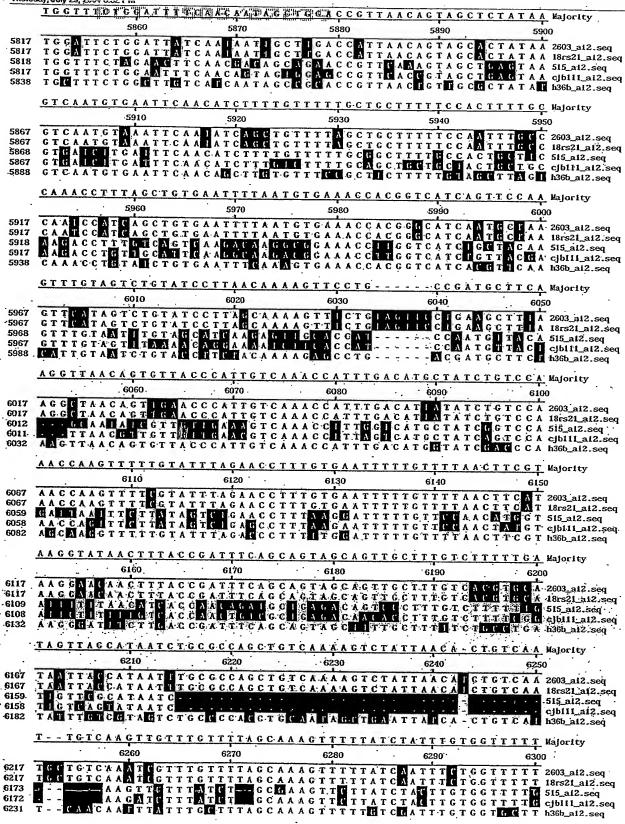


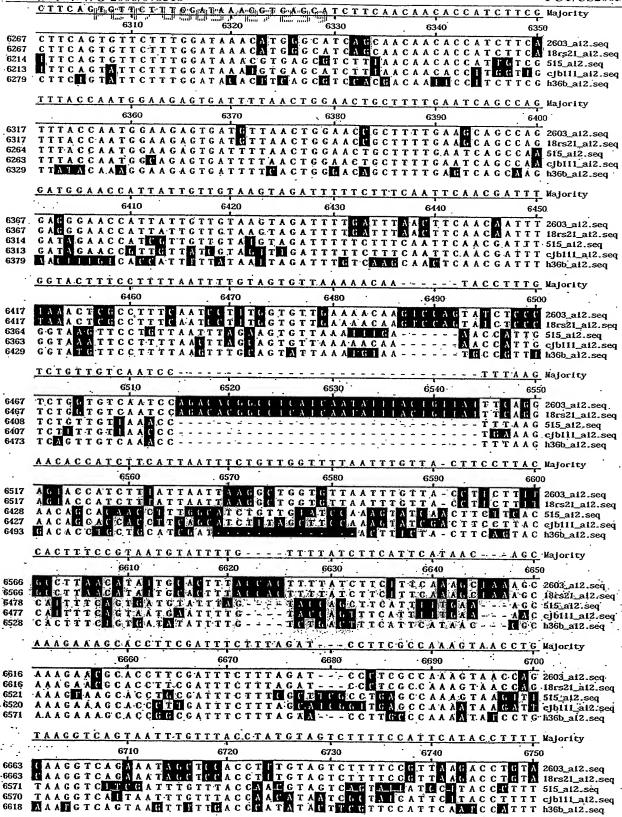


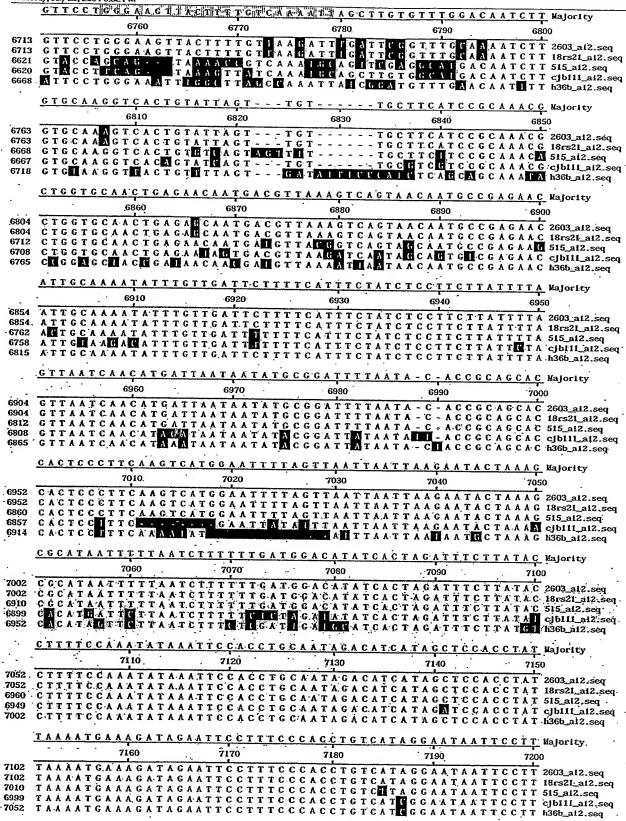


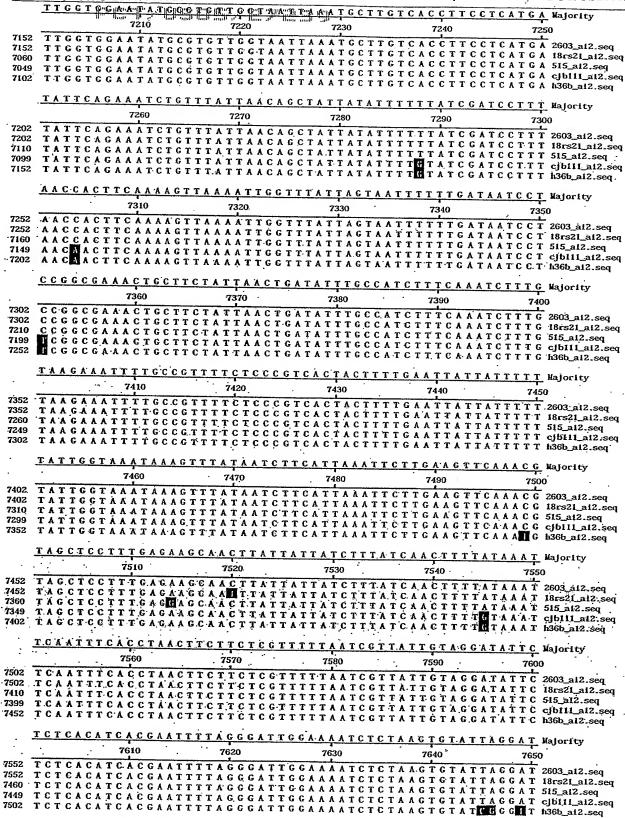


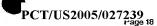


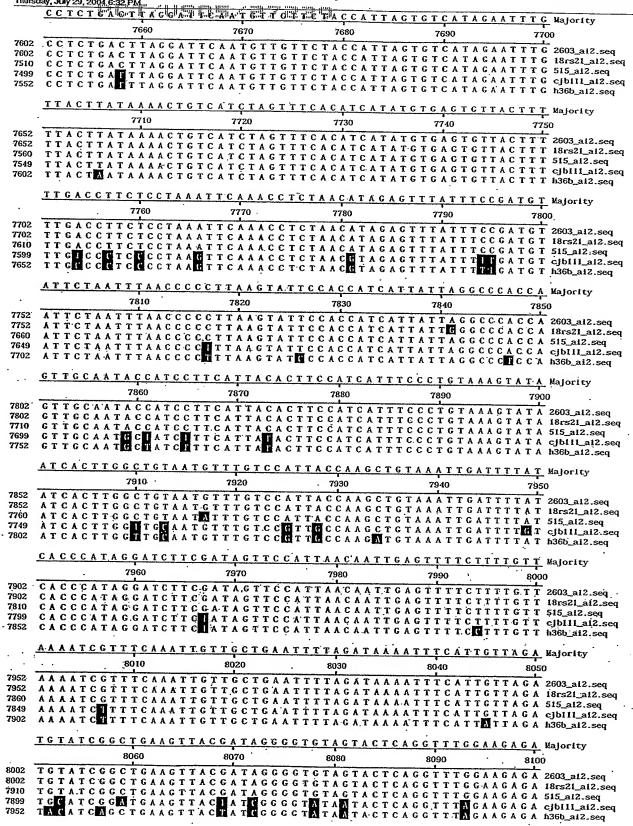


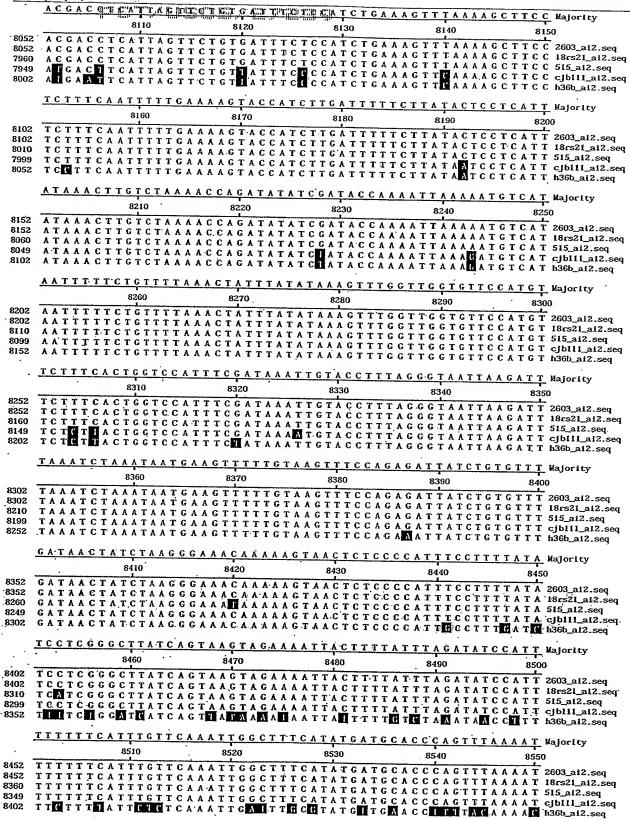








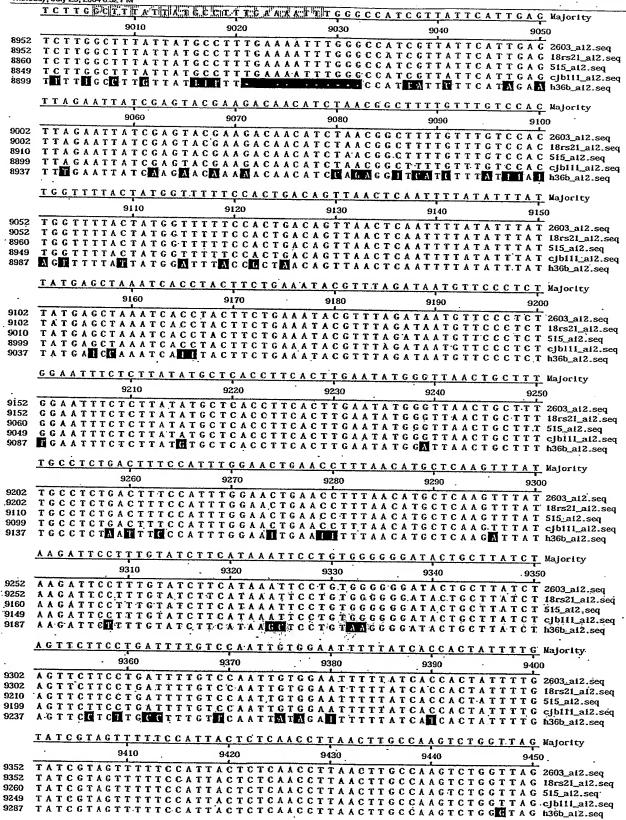


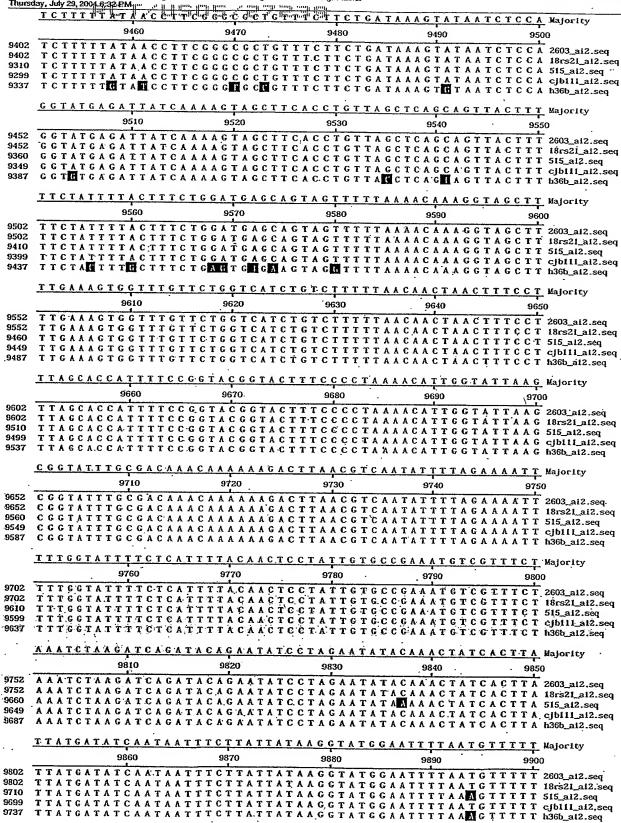


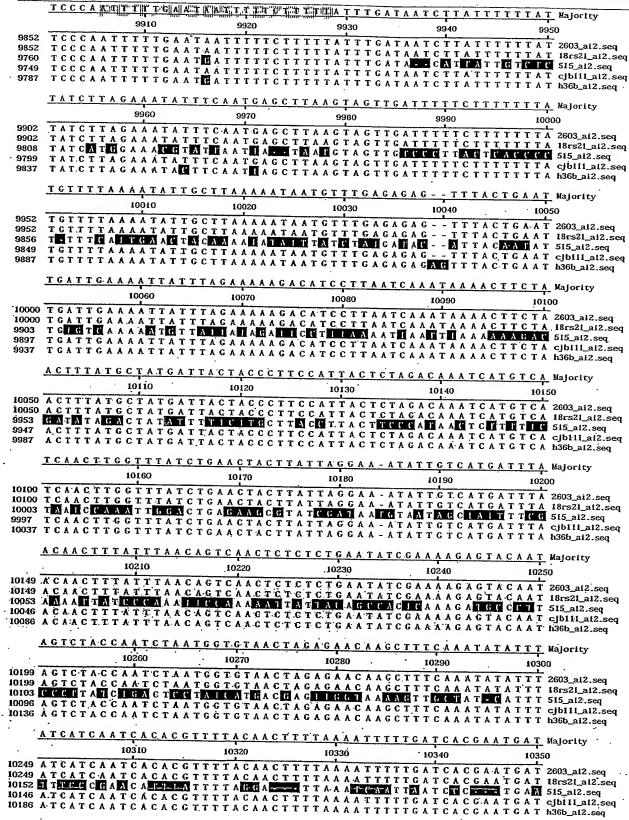
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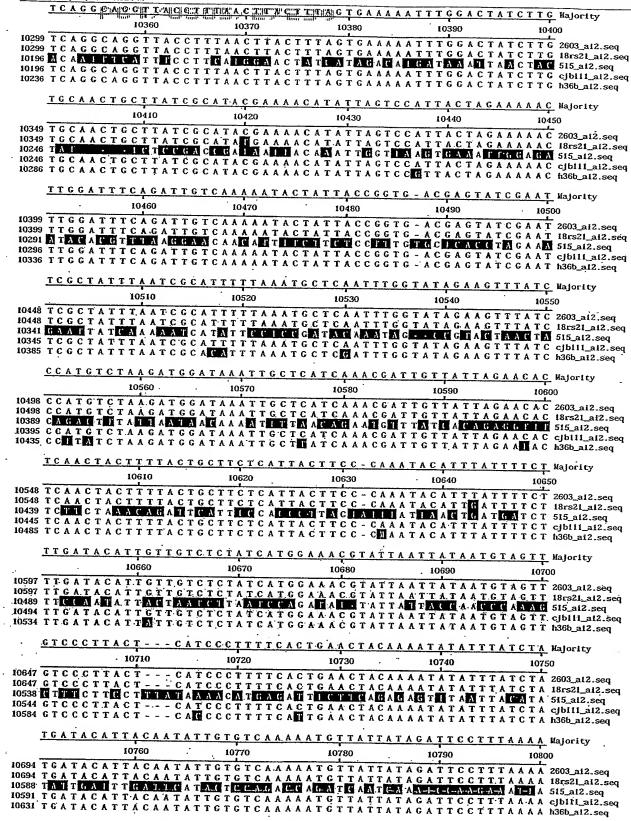
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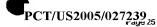
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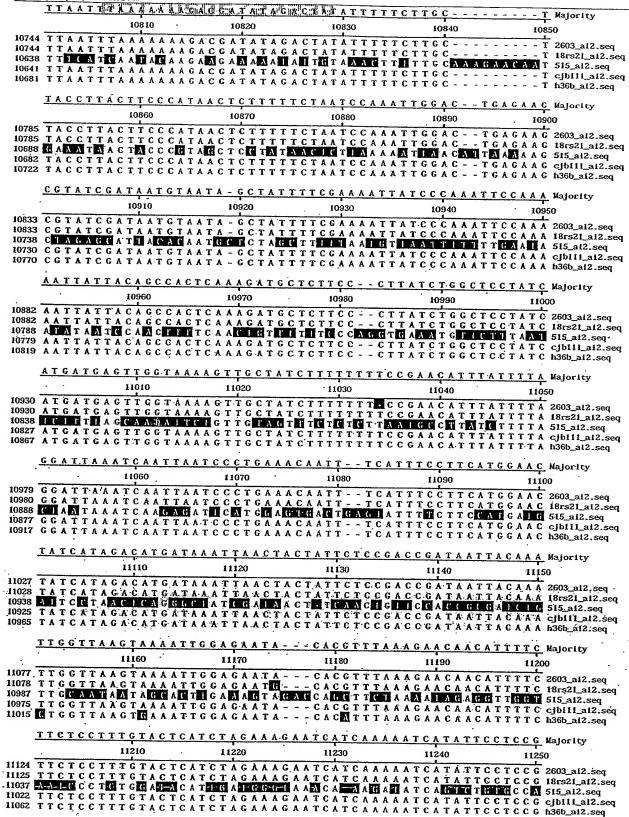


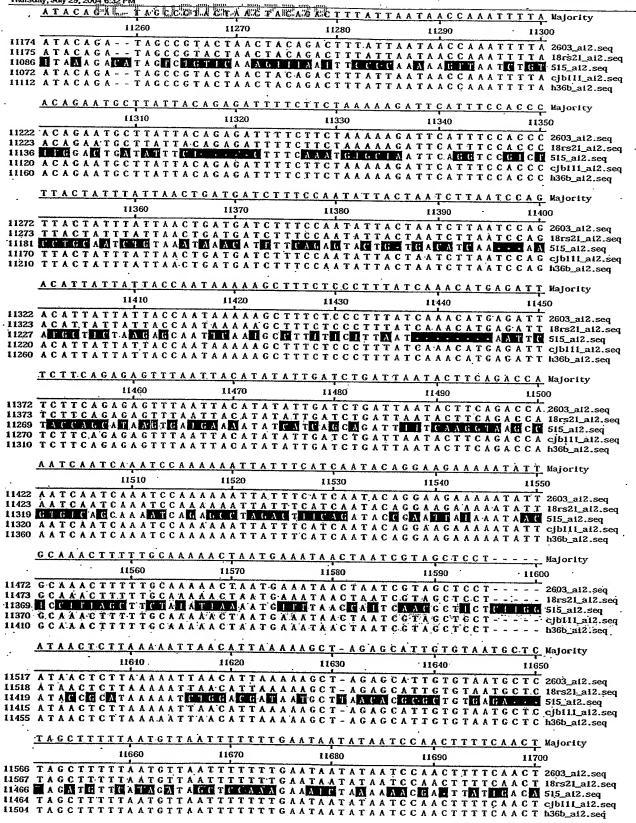


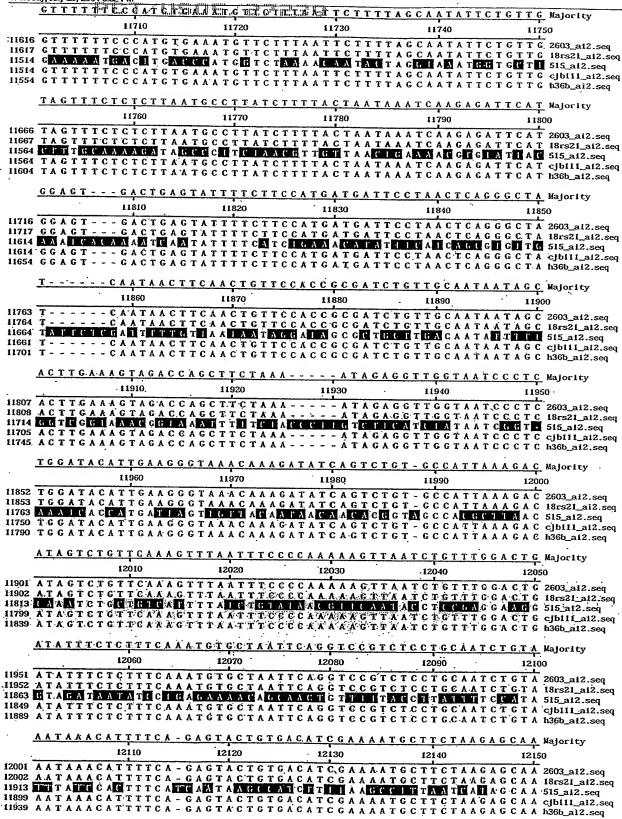




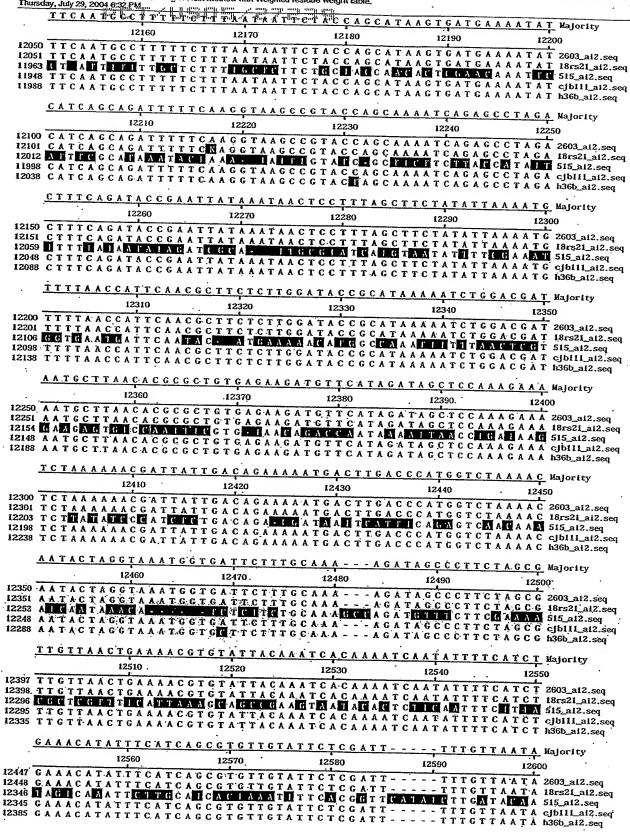


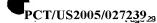


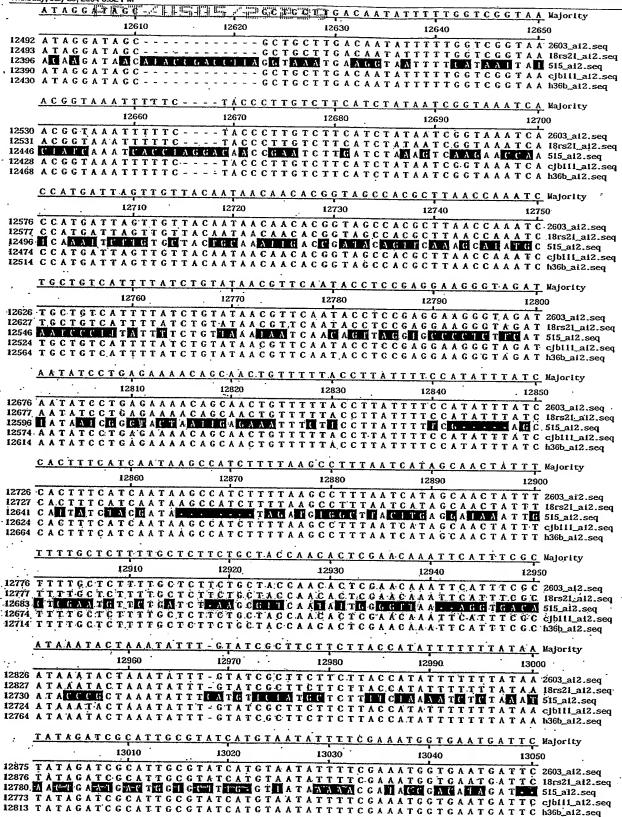




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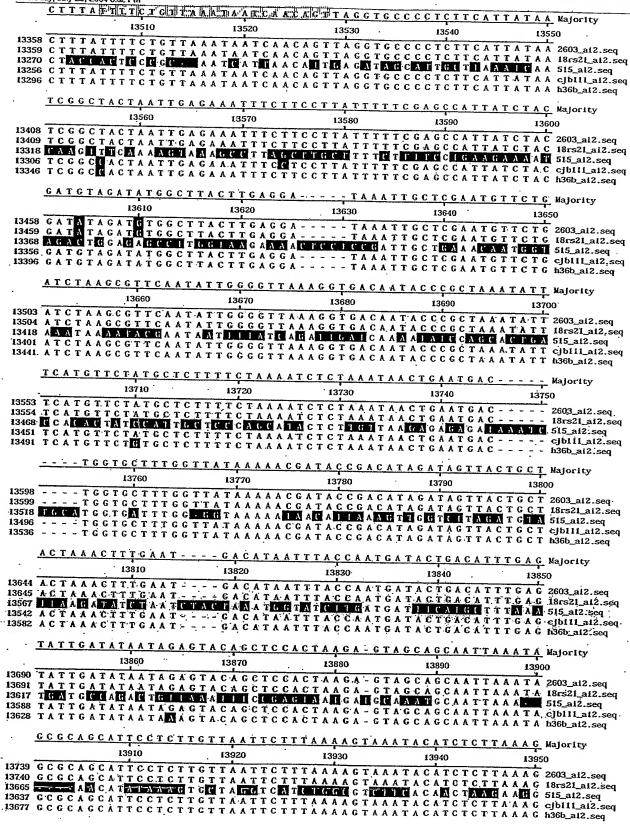






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	ICGIAAC			TAACTTAGCATGGGTATTGGT	A A A A T T Majority
52	TCGTAAC	GCTCTTT	170	180 190	.200
151		GCTCTTT	A A T T A T C T C T A A T T A T C T C T	T A A C T T A G C A T G G G T A T T G G T T A A C T T A G C A T G G G T A T T G G T	A A A A T T 2603_ai2.seq A A A A T T nem316 ai2.seq
	TTGAAAA	TAGACTA		AACCTCGGGCCÁCTTT-CTAT	
		210	220	230 240	250
102	TTGAAAA	TAGACTA	AGTATTATI	MACCICACCICTACTAT	C.C.A.T.C.A. DCCC
201	TTGAAAA	TAGACTA	AGTATTATI	TAACCTCGGGCCACTTTCTAT	G C A T G A nem316_ai2.seq
	AATCAAT	TTCTTTA	TAGAATTGTT	CACGAATAGGAGCTTCTGGA	G C A A C T Majority
		260	270	280 290	300
152 251	AATCAAT	TTCTTTA	T	CACGAATAGGAGCTTCTGGA	G C A A C T 2603_a12.seq
	•				
:	KINGUNI	CCCCTGA	320	GTGCAAAAGTGCATCCTCC	TCTAGC Majority
202	ATAGCAT			330 340 GTGCAAAAGTGCACCCTCC	350
301	ATAGCAT	CCCCTGA	A C C A G A A A C'T	GTGCAAAAGTGCATCCTCC	TCTAGC 2603_ai2.seq TCTAGC.nem316_ai2.seq
٠				GTCAAAACCAGCATCTATAG	•
		360	370	380 390	400
252 351	AACTGTT		TGTTAGGACA	GTCAAAACCAGCATCTATAG	G T A A T T 2603_ai2.seq
331		CCGTCTC	I GIIA G G A C A	GTCAAAACCAGCATCTATAG	GTAATT nem316_ai2.seq
٠,	TAAATAT		CCAAAGAGTT	CTCGATAATAATCATTAATC	GCACGA Majority
		410	. 420	430 440	. 450
302 401		TTTTTCT	C	C.T.C.G.A.T.A.A.T.C.A.T.T.A.A.T.C.C.T.C.G.A.T.A.A.T.C.C.T.C.G.A.T.A.A.T.C.C.T.T.A.A.T.C.C.T.C.A.T.T.A.A.T.C.C.T.C.C.T.T.A.A.T.C.C.C.T.C.A.T.T.A.A.T.C.C.T.C.A.T.T.A.A.T.C.C.T.C.A.T.T.A.A.T.C.C.T.C.A.T.T.A.A.T.C.C.T.C.A.T.T.A.A.T.C.C.T.C.A.T.T.A.A.T.C.C.T.C.A.T.T.A.A.T.C.C.T.C.A.T.T.A.A.T.C.C.T.C.A.T.T.A.A.T.C.C.T.C.A.T.T.A.A.T.C.C.T.C.A.T.T.A.A.T.C.C.T.C.A.T.T.A.A.T.C.C.T.T.A.A.T.C.C.T.C.A.T.T.A.A.T.C.C.T.C.A.T.T.A.A.T.C.C.T.T.A.A.T.C.T.T.A.A.T.C.T.T.A.A.T.C.T.T.A.A.T.C.T.T.T.A.A.T.C.T.T.T.A.A.T.C.T.T.T.A.A.T.C.T.T.T.A.A.T.C.T.T.T.A.A.T.C.T.T.T.A.A.T.C.T.T.T.A.A.T.C.T.T.T.A.A.T.C.T.T.T.A.A.T.C.T.T.T.A.A.T.C.T.T.T.A.A.T.C.T.T.T.T	G C A C G A 2603_ai2.seq
	- IRRCUII	460	470	TATCACAATTTTAACTAAAA1	•
352	TAACGTT	1:		480 490 TATCACAATTTTAACTAAAA	500
151	TAACGTT	TTTTCAT	GGATAATTG	TATCACAATTTTAACTAAAA	AACCT 2603_a12.seq AACCT nem316_ai2.seq
				GATTGGAACGTCAGTTAGTC	
		510	520	530 540	550
102	CACTACT	ACAATAAA	ACTAAAAA	GATTGGAACGTCACTTACTC	C (4 T C 2002 - 12
501	·OKCIKCI	A CARIARA	CACIIAAAAA	GALLEGRACGTCAGTTAGTCC	CAATC nem316_a12.seq
	TTTTTT	TACTTCAC	TTTCTTTAA	C C A A T C C T T G G C T A A A A A G A T	ATACC Majority
		560	570	580 590	. 600
52 51	TTTTATT	TACTTCAC	TTTCTTTAA	C C A A T C C T T G G C T A A A A A G A T	A T A C G 2603_a12.seq
				C'CAATCCTTGGC.TAAAAAGAT	
	CAGTTAG			C A A G T A T A A A A C C A G C T A A A A	CATCT Majority
502	CAGTTAC	610 4 T T C A A A A	620 TACCATAA	630 640	650
01	CAGTTAG	A T T C A A A A	TACCATAAG	C A A G T A T A A A A C C A G C T A A A A C A A G T A T A A A A C C A G C T A A A A	CATCT 2603_a12.seq

	inment Report CY, Q_	Hein method with Weighted	residue weight table.		FC1/US2003/0
	GTCGGAAA"ATGAA"C	CCTAGGTAA	ATA CGAGATAA	20044774444	
	660	670	680	690	•
552		CCCTAGGTAA	ATACCICATA		700
651	GTCGGAAATGAAC	CCCTAGGTAA	ATACGAGATAA		A A T nem316_a12.seq
	GAGCAAACCCAAAG	TACCTTGGCA	CAACAGTTTCCA	A T A T A C T C T T A G	G.C.A. Natanteu
	710	720	730	. 740	750
602 701		TACCTTGGCA	CAACAGTTTCC	TATACTCTTAG	
		I HOUTI GGC A	CARCAGIITECA	TATACTCTTAG	G C A nem316_a12.seq
	TATAGTACTCCAAT	AAAATAATAA	TACTCCCAAATA	TCATAAATGTT	CCC Majority
652	760	770	780	790	800
751		A A A A T A A T A A T A A A A T A A T A A T	TACTCCCAAATA	TCATAAATGTT	C C C 2603_ai2.seq
	ATCGAGTGCCCACT	GGCAAAGGAA	n i o o o o o o o o o o o o o o o o o o	I CAIAAA I G []	CCC nem316_a12.seq
	ATCGAGTGCCCACT	820			•
702	ATCGAGTGCCCACT	GGGAAACGAA	830 FACCCACCTCC	840	850
801	ATCGAGTGCCCACT	G G G A A A C G A A 1	T A G C C A C C T G C A		G G T 2603_a12.seq G G T nem316 a12.seq
	TAAAGTTGGTCTTA	CTCTTTGAAAA		A C A A A C T A T A C	4.77.4.17.4
	860	870	880	890	900
752 851	TAAAGTTGGTCTTA	CTCTTTGAAAA	ATAAGTTTTAA		
. 651			CALARGITITAA	AGAAAGTATAC	ATA nem316_a12.seq
	TACCAGAGATAATA	G C A T T T A C T G C	GATAAATCTAG	CTTGAGGATAC	CAC Majority
909	910	920	930	940	950
- 802 -901	T A C C A G A G A T A A T A (T A C C A G A G A T A A T A (G C A T T T A C T G C G C A T T T A C T C C	GATAAATCTAG	CTTGAGGATAC	C A C 2603_a12.seq
-	TTCTTAAGGTAACAG			-	G C T Majority
852	TTCTTAAGGTAACAG	970 ,	980	990	1000
951	TTCTTAAGGTAACAG	GAAAGTGACGC	TCATAATCGCA	A T A G C T A T C T G A T A G C T A T C T G	G C T 2603_ai2.seq G C T nem316 ai2.seq
	TACAGTATTACCAAT	CACAGTGATT	AACTTGAAAAA	T C T T C T A C A A A	C.A. T. Hata-ta-
	1010	1020	1030 .	1040	1050
902 1001	TACAGTATTACCAAT	CACAGTGATT	AACTTGAAAAA	TCTTGTAGAAA	
			ARCIIGAAAAA	T C T T G T A G A A A	GAT nem316_a12.seq
•	TTGGCAACTGTCCTC	TAACACTTTC	TTGAATGTTTT	GGTCAAATGCAA	TT Majority
952	TTCCCAACTCCTC	. 1070	1080	1090	1100
1051	TTGGCAACTGTCCTC TTGGCAACTGTC.CTC	TAACACTTTC	TTGAATAGTTT	G G T C A A A T G A A	T T 2603_ai2.seq
٠.					
	ACAGTGTCGGCCAA	. 1120			•
1002	A C A G T G T C G G G C C A A	TATTCATCA	1130 C C A A T C C T A A A	, 1140	1150
1101	ACAGTGTCGGGCCAA	TATTGATGA	CCAATCCTAAA	C T G A A A A A T A A (A T 2603_ai2.seq A T nem316_ai2.seq
	AATAGCAATAAATGC	TTGAATAAGT	TTACTATTTTC	CGAGATAACAT	T A Madawater
· · ·	1160	1170	1180	1190	1200
1052	AATAGCAATAAATGC AATAGCAATAAATGC	TTGAATAAGT	TTACTATTTTG	100101511	
1151		- I OMA I ARGI	TINCINITIE	A C G A G A T A A C Ă 1	TA nem316_ai2.seq
•	GTCTTTTTATATCTT	TCTAATATTG	GCAAACAAGCCA	CGTAAGTTAGA	T A Majority
***	1210	1220	1230	1240	1250
1102 1201	GTCTTTTTATATCTT GTCTTTTTATATCTT	TCTAATATTG	GCAAACAAGCCA	CGTAAGTTAGA	T A 2603_a12.seq
			GCAAACAAGCCA	CGTAAGTTAGA	TA nem316_a12.seq
	GAAAACAATC GAAAT	TAAAATTCCCT		AATGGAATAAC	C A Majority
1152	GAAAACAATCCAAAT	1270 T A A A A T T C C C C	1280	1290	1300
1251	G A A A A C A A T C G A A A T G A A A A C A A T C G A A A T	TAAAATTCCCT	I C A A C G A T A T T A I C A A C G A T A T T A	AATGGAATAAC	C A 2603_a12.seq

Trunsday, July 29, 2004 646 PM CTAATTCCCCTACCACCAATAAATGTTCTGATATCAAAGTTA Majority 1310 1320 1330 1340 TTGTTAAAAGGTAATTGCCTACACCAATAAATGTTCTGATATCAAAGTTA 2603_ai2.seq 1202 TTGTTAAAAGGTAATTGCCTACCAATAAATGTTCTGATATCAAAGTTA nem316_a12.seq GCAAATATAGCATACAAAGGAATCGCAAAGACATAGTTGAGAGCTACCAT Najority 1370 1380 1390 G C A A A T A T A G C A T A C A A A A G G A A T C G C A A A G A C A T A G T T G A G A G C T A C C A T 2603_a12.seq 1252 G C A A A T A T A G C A T A C A A A G G A A T C G C A A A G A C A T A G T T G A G A G C T A C C A T nem316_a12.seq 1351 A G A T A C G G T C A A G C T A A C T G T A C C A A A T A G A C T A G C T T T A A T A A A A T C T T Majority 1410 1420 1430 1440 1450 1302 A GATA C G G T C A A G C T A A C T G T A C C A A A T A G A C T A G C T T T A A T A A A A T C T T 2603_a12.seq
1401 A G A T A C A G C T A A C T G T A C C A A A T A G A C T A G C T T T A A T A A A A T C T T nem316_a12.seq TTGCACTCTCTATTTTCCAGAAAATAGCGAAACTTGCTAAAAATAAA Majority 1460 1470 1480 1490 1500 1352 TTGCACTCTCTATTTTCCAGAAAATAGCGAAACTTGCTAAAAATAAA 2603_a12.seq TTGCACTCTCTATTTTCCAGAAAATAGCGAAACTTGCTAAAAATAAA nem316_a12.seq GCTAGAGCAACCATATTCATCGGTAAACCGATAAAGGTTTCTGGACCACG Najority 1530 1540 1550 1402 GCTAGAGCAACCATATTCATCGGTAAACCNATAAACGTTTCTGGACCACG 2603_a12.seq . 1501 · G C T A G A G C A A C C A T A T T C A T C G G T A A A C C G A T A A A G G T T T C T G G A C C A C G nem316_a12.seq ATTAGCAAGTATAACTTTTAAAAAGTGATCTTAATAAGAGTACACCATAAC Majority 1560 1570 1580 1590 1600 1452 ATTAGCAAGTATAACTTTTAAAAGTGATCTTAATAAGAGTACACCATAAC 2603_ai2.seq ATTAGCAAGTATAACTTTTAAAAGTGATCTTAATAAGAGTACACCATAAC nem316_ai2.seq TTGATTTCAAATCAAATAAAAAAAAAAAGCAACTAACATCGGAAGGATTGAA Majority 1630 1610 1620 1640 1650 TTGATTTCAAATCAAATAAAATAAAAGCAACTAACATCGGAAGGATTGAA 2603_ai2.seq TTGATTTCAAATCAAATAAAATAAAAGCAACTAACATCGGAAGGATTGAA nem316_ai2.seq 1502 A A A T C A A C C T T T A A A A A T T C T G C T C C T G G T A T T A A T G G A A A T G A A A C C A T Majority 1660 1670 1680 1690 1700 1552 AAATCAACCTTTAAAAATTCTGCTCCTGGTATTAATGGAAATGAAACCAT 2603_a12.seq
1651 AAATCAACCTTTAAAAATTCTGCTCCTGGTATTAATGGAAATGAAACCAT nem316_a12.seq 1552 CATCAATACAAAAGATAAGGCAGAAAGAATGGCGATTGTCACCATTTTAC Majority 1750 1710 1720 1730 1740 . CATCAATACAAAAGATAAGGCAGAAAGAATGGCGATTGTCACCATTTTAC 2603_a12.seq 160Ź CATCAATACAAAAGATAAGGCAAGAAAGAATGGCAATTGTCACCATTTTAC nem316_a12.seq 1701 1770 1760 1780 1790 CTGTATTTGTCATAAAAAAATTCCTCCAATTTAAAATTGAAAGAAGC nem316_a12.seq 1751 T.C.C.A.A.A.G.C.T.A.A.G.C.G.T.A.C.G.C.G.A.A.A.A.A.A.C.C.T.T.G.T.C.T.C.T.C.C.C.A.T.G.C. Majority . 1820 1830 1810 -1840 1850 TCCAAAGGTAAGCGTATGTACGCGAAAAAAACCCTTTGTCTCCCCATCC 2603_a12.seq. 1702 TCCAAAGGTAAGCGTAE GTACGCGAAAAAAAACCTTTGTCTCCCCATCC nem316_a12.seq 1870 1860 · 1880 . 1890 . 1900 1751 A G A C T T T A C T C T C G G T T G T G G A A T C T C A C C A C A T C A G C T T T C G C T C G C G G 2603_ai2.seq A G A C T T T A C T G T C G G T T G T G G A A T C T C A C C A C A T C A G C T T T C G C T C G C G G nem316_a12.seq A-CTGATGCTTCACAACTGACAAATAAGTTCGAAGCGATTACCGCCGGTCG Majority 1910 1920 1930 1801 ACTGATGCTTCACAACTGACAAATAAGTTGGAAGCGATTACCGCCGGTCG 2603_ai2.seq

A C T G A T G C T T C A C A A C T G A C A A A T A A G T T G G A A G C G A T T A C C G C C G T C G nem316_a12.seq

1901

Thurse	(ay, July 29, 2004, 6/46, FM)	
	GGAATTAGACCCTGCCTCACCTCAAGACATATAGCATAACAAAAAAACTTG Majority	
	1960 1970 1980 1990 2000	
1851	GGAATTACACCCTGCCCTGAAGACACCTATAGCATAACAAAAAAACTTG 2603_a12.seq	
1951	GGAATTACACCCTGCCCTGAAGACACCTATAGCATAACAAAAAACTTG zoos_atz.seq	20
		~1
	C A A T T G C A A G T T T T T T A A T T A C T A A T T A G T A G T A G T G A T T A A A A	
	2010 2020 2030 2040 2050	
1901	CAATTGCAAGTTTTTAATTACTAATTAGTAGTGATTAAAAATCATA 2603_a12.seq	
2001	CAATTGCAAGTTTTTAATTACTAATTAGTAGTAGTGATTAAAAATCATA nem316_a12.se	έġ
		•
	TTAATACCAAATTACTATGCTGTATCGTTTCTTTCAGATTTGCTATTTT Majority	
	2060 2070 2080 2090 2100	
1951	TTAATACCAAATTACTATACTATACTATCGTTTCTTTCAGATTTGCTATTTTT 2603_a12.seq	
2051	TTAATACCAAATTACTATGCTGTATCGTTTCTTTCAGATTTGCTATTTT nem316_a12.se	pq.
		-
•	AGTTTTTCTTAAAAAGATAAACAAATTCCCAAAATAATACAACCAAGAA Najority	
	2110 2120 2130 2140 2150	
2001	AGTTTTTCTTAAAAAGATAAACAAAATTCCCCAAAATAATACAACCAAGAA 2603_a12.seq	
2101	A-G T T T T T C T T A A A A A G A T A A A C A A A A T T C C C A A A A T A A T A C A A C C A A G A A nem316_a12.se	:q
	TTC TC A C TC C T C C A C C A A T A A T C A T T C C T C T	
	TTGTCAGTCCTCCACCAATAATCATTCCTGTTTTAGGAAGAATGATTGT Najority	
	2160 2170 2180 2190 2200	
2051	TTGTCAGTCCTCCACCAATAATCATTCCTGTTTTAGGAAGAAATGATTGT 2603_a12.seq	
2151	TTGTCAGTCCTCCACCAATAATCATTCCTGTTTTAGGAAGAAATGATTGT nem316_a12.se	p;q
	G G A A A A G C G G T T G T G A T G G T T T A G G A T T T G T T G G T G G A G C A G T T T C T T T Majority	
2101 2201	GGAAAAAGCGGTTGTGATGGTTTAGGATTTGTTGGTGGAGGAGTTTCTTT 2603_a12.seq	
LEGI	G G A A A A G C G G T T G T G A T G G T T T A G G A T T T G T T G G T G G A G G T T T C T T T nem316_a12.se	;q
	TTCGTTTTCTACCTCTACTTCCTGTGTTTTATTACCAACTACAGCAACTA Majority	
	2260 2270 2280 2290 2300	
2151	TTCGTTTTCTACCTCTACTTCCTGTGTTTTATTAGCAACTACAGCAACTA 2603_a12.seq	
2251	TTCGTTTTCTACCTCTACTTCCTGTGTTTTATTAGCAACTACAGCAACTA 2003_a12.seq	eg.
•		
	CAGCATCCTTCATAGATATACGGTAACCAGTTAGTGCTTTTGCTTCGA Majority	
	2310 2320 2330 2340 2350	
2201	CAGCATCCTTCATAGATATACGGTAACCAGTTAGTGCTTTTGCTTCTCGA 2603_a12.seq	
2301	CAGCATCCTTCATAGATATACGGTAACCAGTTAGTGCTTTTGCTTCGA nem316_ai2.se	:Q
	A A A A T A T A C T T A C C A G G T A A T A A A C C T T C A A C C T C A A T T T C T C	
	2360 2370 2380 2390 2400	
2251	AAAATATACTTACCAGGTAATAAACCTTCAACCTCAATTTCTCCCTTATC 2603_a12.seq	
2351	AAAATATACTTACCAGGTAATAAACCTTCAACCTCAATTTCTCCCTTATC nem316_ai2.se	q
	ATCAGTTACTAATGAAGTAATCCCATCTTGATCGGTCGTAAATCGTCCAT Majority	
	2410 2420 2430 2440 2450	
2301 2401	ATCAGTTACTAATGAAGTAATCCCATCTTGATCGGTCGTAAATCGTCCAT 2603_ai2.seq. ATCAGTTACTAATGAAGTAATCCCATCTTGATCGGTCGTAAATCGTCCAT nem316_ai2.se	_
	ATOMOTIAN TO A TOTAL TOTAL TO A TOTAL TOTAL TO A TOTAL TOTAL TO A TOTAL T	ų.
	TTTTAAAGCGAACTGGCTGATTCTGGTTATCGTATAATACAAATATTACT Wajority	
	2460 2470 2480 2490 2500	
2351	TTTTAAAGCCAACTGGCTGATTCTGGTTATCGTATAATACAAATATTACT 2603_a12.seg	
2451	TTTTAAAGCGAACTGGCTGATTCTGGTTATCGTATAATACAAATATTACT nem316_ai2.se	ea
•		1
	CCTGATAGCCTTTTCTTTATCTTTCCTTTTTTTTTTATTAATAAGTTT Majority	
	2510 2520 2530 2540 2550	
2401	CCGGATAGCCTTTTCTTTATCTTTCCTTCTTTTGTATATTAATAAGTTT 2603_a12.seq	
2501	CCTGATAGCCTTTTCTTTATCTTTCCTTTTGTATATTTAATAAGTTT nem316_a12.se	p:
		-
•	TAATCGGCCTGTTTCAACTTTTCGCTTAGGATTTATCTGTAATTGATTTG Hajority	
•	2560 2570 2580 2590 2600	
2451	TAATCGGCCTGTTTCAACTTTTCGCTTAGGATTTATCTGTAATTGATTTG 2603_a12.seq	
2551	TAATCGGCCTGTTTCAACTTTTCGCTTAGGATTTATCTGTAATTGATTTG nem316_a12.se	q
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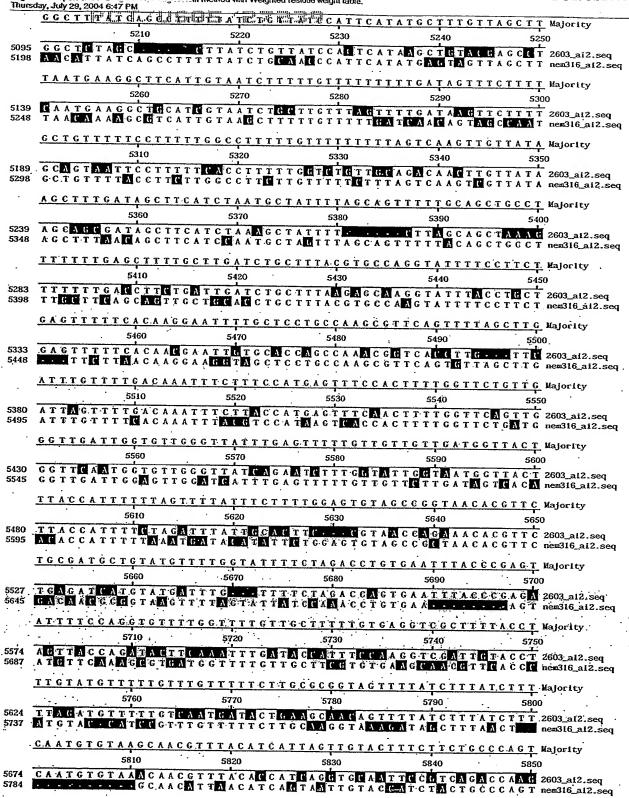
2620 2630 2640 2650 ATAACTTATCATCTGGTAATTCAATATAAAAGGTACTATTGTTGAAACC 2603_a12.seq ATAACTTATCATCTGGTATTTCAATATAAAAGGTACTATTGTTGAAACG nem316_a12.seq CTTTGATCAGCTTTATAAGCACGACCAAAGTACGAACCATTTGGGAGTGC Majority 2660 2670 2680 2690 2700 CTTTGATCAGCTTTATAAGCACGACCAAAGTACGAACCATTTGGGAGTGC 2603_a12.seq CTTTGATCAGCTTTATAAGCACGACCAAAGTACGAACCATTTGGGGAGTGC nem316_a12.seq 2651 TATCTTGTCTGACCATTAGTATCAGTAGGAGAAGTCAAGATACTCTTAT Majority 2710 2720 2730 2740 2750 2601 TATCTTTGTCTGACCATTAGTATCAGTAGGAGAGGTCAAGATACTCTTAT 2603_a12.seq 2701 TATCTTTGTCTGACCATTAGTATCAGTAGGAGAGATACTCTTAT nem316_a12.seq ACTTCTGGTTCAATTCGCTATCTGTCATTTGGCTCAATAAATCAACTTTT Majority 2651 ACTTCTGGTTCAATTCGCTATCTGTCATTTGGCTCAATAAATCAACTTTT 2603_a12.seq A C T T C T G G T T C A A T T C G C T A T C T G T C A T T T G G C T C A A T A A A T C A A C T T T T nem316_a12.seq 2751 AAGTTGTCAGTCACAGTCCATAAACGATAAGAAATCCCCTCTGTAGT Majority 2810-2820 2830 2840 2850 2701 AAGTTGTCAGTCACAGTCCATAAACGATAAGAAATCCCCTCCTCTGTAGT 2603_a12.seq A A G T T G T C A G T C A C A G T C C A T A A A C G A T A A G A A A T C C C C T C T C T G T A G T nem316_a12.seq 2801 . ATTTGGCTGAAGTCCTATCTGTGTGATTGTTAGTTGATTAGGGGGTATCAG 2900 2860 2870 2890 2880 ATTTGGCTGAAGTCCTATCTGTGATTGTTAGTTGATTAGGGGGTATCAG 2603_a12.seq ATTTGGCTGAAGTCCTATCTGTGATTGTTAGTTGATTAGGGGGTATCAG nem316_a12.seq CATTTACACTGGCTACCGAAAAAAACGCTAATTGTACCAATCCTAAAAAG Majority 2910 2920 2940 2950 2930 2801 CATTTACACTGGCTACCGAAAAAAACGCTAATTGTACCAATCCTAAAAAG 2603_a12.seq 2901 CATTTACACTGGCTACCGAAAAAACGCTTAATTGTACCAATCCTAAAAG nem316_a12.seq 2970 3000 2980 2990 2851 CCCTTTCTTTTCTCTCTTTAAATTTTCGTTTTAAATATAATAGTAAAGC Majority 3050 3010 3020 3040 3030 2901 CCCTTTCT TTTCTCTCTTTAAATTTTCGTTTTAAATATAATAGTAAAGC 2603_ai2.seq 1008 CCCTTTCTTTTCTCTCTTTAAATTTTCGTTTTAAATTTTCGTTTTAAATATAGTAAAGCnem316_ai2.seq GACTAATATAAGAATAACTAGGATTGATAAGAGAAATAAAGTTTATAGT Majority • . . 3060 3070 3090 3080 3100 GACTAATATAAGAATAACTAGGATTGATTGATAAGGAGGAAATAAAGTTTATAGT 2603_a12.seq 2951 GACTAATATAAGAATAACTAGGATTGATAAGAAAAAAATAAAGTTTATAGT nem316_a12.seq G T G T T T G C A A T T G T T T C A T T A A A T A G T T G T T T T C T T T A A C A G G A G G T A C A Hajortty 3110 . 3150 3001 GTGTTTGCAATTCTTTAAATAGTTCTTTTAACAGGAGGTACA 2603_ai2.seq GTGTTTGCAATTCTTTCATTAAATAGTTCTTTTCTTTAACAGGAGGTACA nem316_a12.seq 3101 TACTTGATTCGATGCCCTCTAACTAGTAAACGATGTGAATTAATCGAATA Majority **-** . 3160 3200 3170 3180 3190 3051 TACTTGATTCGATGCCCTCTAACTAGTAAACGATGTGAATTAATCGAATA 2603_a12.seq TACTTGATTCGATGCCCTCTAACTAGTAAACGATGTGAATTAATCGAATA nem316_a12.seq A G G T G T A C A T G T T A G C A A A G T C G C A T A A T C C T T A C C T T T A A C A A C C A A T A Wajority 3250 3210 3220 3230 3240 AGGTGTACATGTTAGCAAAGTCGCATAATCCTTACCTTTAACAACCAATA 2603_a12.seq 3101 AGGTGTACATGTTAGCAAAGTCGCATAATCCTTACCTTTAACAAACCAATA nem316_ai2.seq 3201

FIGURE 20D

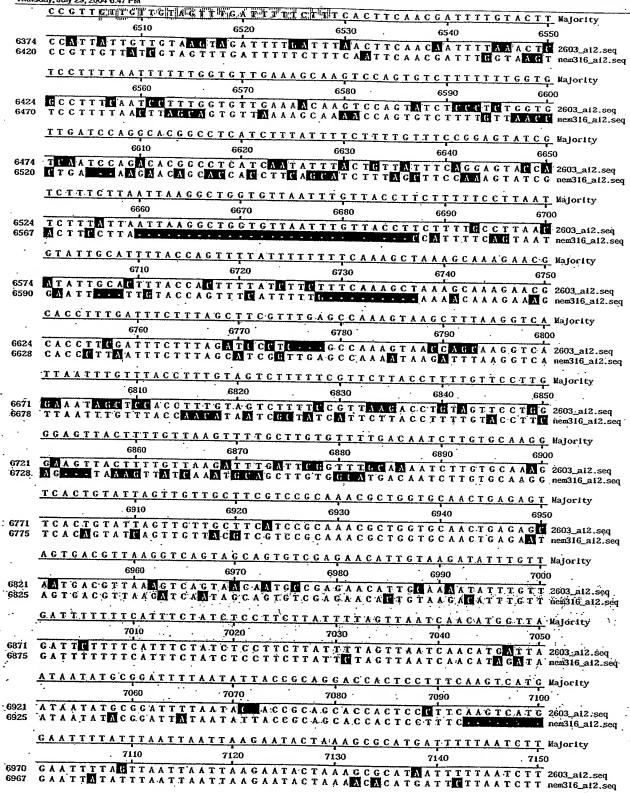
	ATTTATO	Ama ama a 4	TALE OF THE COMM				
		2200	E AND PLOT AND ASSESSMENT	THE PARK WAS A C	TTATTGATCA	ACCTTATAG Majority	
215		3200	3270	3280	3290	2200	
315 325	L ATTTAG	AAAAAT	TATCTGGCT	TTACAACAC	TTATTTGATCA		
525	I AIIIAG	AAAAAT.	TATCTGGC.T	TTACAACAC	TTATTTGATCA	ACCTTATAG 2603_ai2.sec ACCTTATAG nem316_ai2.s	- -
	GCTAAA	A C T T C T 1		T C 4 4 T 4 T 4 T		in the state of th	жų
•		3310		- GARIAIAA	AAATTTTTCC	TTTTTTAAG Majority	
220	0.07.1		3320	3330		3350	
3201 3301	I GCTALA.	A C T T C T T	TTGATATTA	TGAATATAA	AAAATTTTCC	TTTTTTAAG 2603_ai2.sec	
	. GOTRAR	ACTICT;	ITGATATTA	TGAATATAA.	AAATTTTTCC	TTTTTTAAG 2603_ai2.sec TTTTTTAAG nem316_ai2.s	l sea
	TTTATCT	ГАААТСТ	C T A A A T A A	CTTACCTTT	LCCT4400000	GATGAGCTG Majority	
		3360	2220			GATGAGCTG Majority	
3251	TTTATO		3370	3380		3400	-
3351	TTTATCT		CTAAATAA	CTTAGCTTT	LGGTAAGCCGC	GATGAGCTG 2603_al2.seq	
			GIXAAIXX	CITAGCTTT	LGGTAAGCCGC	GATGAGCTG 2603_a12.seq GATGAGCTG nexi316_a12.s	eq
	TGATAAC	AGTATG	TGAACTT	TTCCACCAAT	TEGELAGEAC	GTTCCTTCA Majority	•
		3410	3420	3430		WIICCIICA Majority	
3301	TGATAAC	AGTATO	_			3450	
340 i	TGATAAC	CAGTATO	TGAACTTT	T T C C A C C A A 7	TGGCAAGGAG	GTTCCTTCA 2603_ai2.seq	
				· · · · · · · · · · · · · · · · · · ·	I G G C A ANG G AND	GTTCCTTCA 2603_ai2.seq GTTCCTTCA nem316_ai2.s	eq
	AGGTGTC	CTCCTC	CTTTTTCA	AGAACACTAC	TGGTAGTCCC	C G C A T A G A T Najority	
_		3460	3470	3480	3490	•	
3351	AGGTGTC	CTGCTC	CTTTTTCA	1011010710	7000	3500 C G C A T A G A T 2603_a12.seq	
3451	AGGTGTC	CTGCTC	CTTTTTCA	AGAACACTAC	TGGIAGICCC	CGCATAGAT 2603_a12.seq CGCATAGAT nen:316_a12.se	
	ACCTALT			•	- 4.01.1000	GUALAGA i nem316_ai2.sc	eq
	AGGIAKI	111160	TTGATAGA	GGTATATCA	ATATATCCAA1	TCATTCAG Majority	
		3510	3520	3530	3540	3550	
3401	AGGTAAT	TTTTGC	TTGATAGA	GGTATATCA	ATATATCCAA		
3501	AGGTAAT	TTTTGC	TTGATAGÁ	CGGTATATCA	ATATATCCAAT	TCATTTCAG 2603_ai2.seq TCATTTCAG nem316_ai2.se	2.7
	TAATCTE	AAGCAT	GTGGGCGT	TTC 4 C C 4 4 m		inclusive and a second	4
		3560	<u> </u>		ACCTTTTTTT	CCTTTTTCA Majority	
3451	7 1 4 T 0 m 0		3570	3580	3590	3600	
	TAATCTC	AAGCAT	GTGGGCGT	TTCAGCAAT	ACCTTTTTTT	CTTTTTCA 2603_a12.seq	
				I.I.C.A.U.C.A.A.I	ACCITITITITI	TCTTTTCA nem316_ai2.se	p
	GTATAGG	GATCTG	ATAGGCGGC	TTGGGTCCA	GTGTTCTATTA	TAACCTTT	
	•	3610	3620	3630	•		
3501	G.T A T A G G	GATCTG	ATAGGCGGG	TTCCCCTCCL	3640	3650 T A A G C T T T 2603_a12.seq	
3601	GTATAGG	GATCTG	ATAGGCGGG	TTGGGTCCA	G T G T T C T A T T A	TAAGCTTT 2603_ai2.seq TAAGCTTT nem316_ai2.se	
•	TCCTIA				o . o . i o i k i i k	I A A G C I I I nem316_a12.se	q
	TOUTARE	LAAATI	CGTCTATTA	ATCTCTTTA	GTATTTAATTT	TTGGGTTT Majority	
		3660	3670	3680	3690	3700	
3551	TGCTAAC	TCAAAT	CGTCTATTA	ATCTCTTTA	GTATTTAATTT		
3651	I G C T A A C	TCAAAT	CGTCTATTA	ATCTCTTTA.	GGATTTAATTT	TTGGGTTT 2603_ai2.seq TTGGGTTT nem316_ai2.seq	~
•	GATTATC	AAAGTTA	6 G T T A C T T C	. T. T. 4. T. T. 4. C. C.			1
		3710	NOTINCII G		I T T A A T A T T A T	A G. T. A. C. C. A. A. Majority	
2001	C 1 T T 1 T C		3720	3730	3740	3750	•
3601	GATTATE	A A A C T T	AGTTACTTG	ATTATTAGC	TTTAATATTAT	AGTACCAA 2603_a12.seq	
		•	.,	it is a c	FILARIATIAT	AGTACCAA nem316_ai2.sec	1
-	TTTGAAAT	TAAAAG	ATATGAGG	TTATCAAAA	ACCAACTAAC	A.A.C.A.A.T.A.G. Najority	•
		3760	3770			A.A C A.A I A G Najority	-
3651	TTTGAAA	FAAAACC		3780	3790	3800	
3751	TTTGAAAT	T A A A A G G	ATATGAGG	TTATCAAAA	GACCAACTAAG	A A C A A T A G 2603_ai2.seq A A C A A T A G nem316_ai2.seq	
-	•			- IN I O K K K K K	PRCCHACIANG	AACAATAG nem316_a12.seq	í
•	TATCAGGG	CTACAT	TCATCCAT	CGATTTAAAA	CGACCGATTT	CTTAAGGT Majority	
	·	3810	3820	3830	3840		٠.
370 į	TATCAMG	CCTACAT	TCATCCAT		0.00	3850	
3801	TATCAGGG	CCTACAT	TCATCCAT	C G A T T T A A A A	CGACCGATTT	CTTAAGGT 2603_ai2.seq CTTAAGGT nem316_ai2.seq	
					CONCCENTIT	CITAAGGT nem316_a12.seq	
	I I I CT G A	AATTTT	CCTCCCAT	TATGATTCAA	TTCCTTTCT	AACACTTG Majority	
		3860	3870	3880	3890	3900	
3751	TTTTCTGA	TTTTAA	CCTCCCAT	TATGATTCA	TTCCTTTT		
3851	TTTTCTGA	TTTTAK	CCTCCCAT	TATGATTCAA	TTCCTTTTCT	AACACTTG 2603_a12.seq AACACTTG nem316_a12.seq	
			•	•			

			aulia	-7	
Align	ment Report of JWO 2006/07831	8 n method with Weighted reside	19/48 se weight table.	J	PCT/US2005
1 faun	CTAAA D'GATTTTT	I CACICT TEACT	TTATTACC	1 1 1 C T 1 1 C C 1 1	204 4
	3910	3920	3930	3940	3950
3801 108E	CTAAACGATTTTT CTAAACGATTTTT	T G A C G T T G A C G T T G A C G T T G A C G T	T T T.A T T A A C C T T T A T T A A C C	A A A G T A A C C A A A	<u>ــــــــــــــــــــــــــــــــــــ</u>
	ATAATAACTAAAGA				
	3960	. 3970	3980	3990	4000
3851 3951	ATAATAACTAAAGA ATAATAACTAAAGA	TATATAGAATAG TATATAGAA A AG	A T A T C T A T A A A A T A T C T A T A	A T C G T G T T T A A A	A T G 2603_ai2.seq A T G nem316_ai2.seq
	ACCTTCTTTTATTA				
	4010	4020	4030	4040	4050
3901 4001	ACCTTCTTTATTA	ATTTTTCATCAA:	TAGGACCTTT TA <mark>A</mark> GACCTTT	ATAAGGGATAC ATAAGG <mark>A</mark> ATAC	A T 2603_a12.seq A T nem316_a12.seq
	GTCCCCTTACTAAA				
	4060	4070	4080	4090	4100
3951 4051	GTCCCCTTACTAAA GTCCCCTTACTAAA	L G T C T G T G T G T A 1 L G T C T G T G T G T A 1	TTGATCATAA?	CCGGGGTGCAAC	T 2603_ai2.seq
	AATAAGGTTGCATAA				
	4110	4120	4130	4140	TT Majority
4001 4101	AATAAGGTTGCATAA	TCATGTCCAGG	ACAACCAACA	447272	
4101	ARTARUGII GCAIRA	'ICAIGICCAGG	A C A A C C A A-C A	I A A T C T G A A A A G	T T nem316_a12.seq
	ATCGGGTGTAACGAC		•	GCTATCGTTTC	T T Majority
4051	ATCGGGTGTAACGAC	4170 TTTTATCTGATC	4180	4190	4200
4151	ATCGGGTGTAACGAG	TTTTATCTGATO	TACTIGATAT STACTTGATAT	GCTATCGTTTC GCTATCGTTTC	TT 2603_a12.seq TT nem316_a12.seq
	TTATGTTTTGAATAT				_
	4210	4220	4230	4240	4250
4101 4201	TTATGTTTTGAATAT	AAAACTTATCTC	CTTTTTTAA	CTTTTTAAGGT	T A 2603_a12.seq
	G A A A A G A G T T C T T T A				
	4260	4270	4280	4290	4300
4151 4251	GAAAAGAGTTCTTTA	TCTGGAATTCCT	GANTGCGCTG	TTATAGE	
4231		TOTOGRAFIECT	GAGIGGGCTG	TTATAACGGTA	T G nem316_a12.seq
	TGTGCTATTTCCTCC	AATTGGAAGAGA 4320.		•	T C Majority
4201	TGTACTATTCCCCCC	AATTGGAAGAGA	4330 G G T A C C T T C T	4340 .	4350
4301		AAIIGGAAGAGA	MGTACCTTCT	AAATGCCCTGC	T C nem316_ai2.seq
	CTTTAGATAGAACTT 4360	4370	<u>CTGCAAATAT</u> 4380	•	
4251	CTTTAGATAGA.ACTT	CTTGACTTGAAC	CTGCALATAT	4390 A G G G A G T T T T T	4400
4351	CTTTAGATAGAACTT	CTTGACTTGAAC	CTGCAAATAT	AGGGAGTTTT	G A nem316_a12.seq
•	CCTATCTTAGGAACT	GAAATTGTTCCG	ATTTTTCAC	TTACCTCTAAC	A T Najority
	4410	4420	4430	4440	4450
4301 4401	C C T A T C T T A G G A A C T C C T A T C T T A G G A A C T	G A A A T T G T T C C G G A A A T T G T G C C G	A T T T T T T C A C A T T T T T T C A C	TTACCTCTAAC TTACCTCTAAC	A T 2603_ai2.seq A T nem316_ai2.seq
•	ACGGGCGTACTCTGC	TACCCCCTTTTG	AATTCGTTTT	TTCTCATAAGG	A T Majority
	4460	. 4470	4480	4490	4500
4351 4451	ACGGGGGTACTCTGC ACGGGGGTACTCTGC	TACCCCCTTTTG TACCCCCTTTTG	A A T T C G T T T T A A T T C G T T T T	TTCTCATAAGG TTCTCATAAGG	A T 2603_a12.seq A T nem316_a12.seq
	CTTCAAGATGGACAT		•		•
	4510	4520	4530	4540	4550
4401 4501	CTTCAAGATGGACAT	TATTTAAAGAAT	CATTATAAGC	TTGTGCTAGAG	C 2603_a12.seq
	CTTCAAGATGGACAT	INIIIAAGAAT	CATTATAAGC	TTGTGCTAGAG	F C nem316_ai2.seq

			9	5/487		
Aligna	nent Report of AWO 2006/ day, July 29, 2004 6:47 PM		elighted residue weight ta	ble.	PCT/U	US20
	ATACGTCCATT	CATTO	T C A C T A A C T 1	TTTTAGCAGC	TCTCTCAAA Kajority	,
	4560	4570	4580	•	4600	٠
4451 4551	A T A C G T C G A T T A T A C G M C G A T T		T G A C T A A G T 1 T G A C T A A G T 1	TTTTTAGCAGC TTTTTAGCAGC	TCTCTCAAA 2603_ai2. TCTCTCAAA nem316_ai	.seq 12.seq
			-	TAGTAAAAAC	GTGATACCA Majority	·
4501	ATCCTGTGTTT	4620	4630	4640	4650	
4601	ATCCTGTGTTT	GATTATTAGA	TICTATEGTA	TAGTAAAAAC	GTGATACCA 2603_ai2. GTGATACCA nem316_ai	i2.seq
		AAAATAGATA	GACCTATTAG	AAAAGAATG	ATAAAAGGA Majority	
455	4660	. 4670	4680	4690	4700	
4651	C T G G A T A C A A T C T G G A T A C A A T	AAAATAGATA	G A C C T A T T A C G A C C T A T T A C	A A A A A G A A T G A A A A A G A A T G	ATAAAAGGA 2603_a12. ATAAAAGGA nem316_a1	.seq 12.seq
	AGATTTGACTT	CTTCTTTTTT	TTTCTTTTT	TGTTGATTTT	TTTAGTCTT Hajority	
4004	4710	-4720	4730	4740	4750	
4601 4701	AGATTTGACTT		T T T G T T T T T T T T T T T T T T T T	TGATGATTTT TGTTGATATT	TTTAGTCTT 2603_ai2. TTTAGTCTT nem316_ai	
	CACGTCATCTC	CTAGATAATG	<u>сстеттестт</u>	ATGATCTAAG	GTACTTCT Majority	
	4760	4770	4780	4790	4800	
4651 4748	CACGTCATCTC	CTAGATAATG CTAMATAATG	G C T C T T G C T T G C T C T T G C T T	ATGATCTAAG ATGATCTAAG	AGTACTTCT 2603_ai2.	.seq 12.seq
	ACTGAAATACC	CTTAGATCAT	AAGCAC'AGCT	TTAACTGTGC	TATACATC Hajority	
	4810	4820	4830	4840	4850	
4701 4798	ACT G A A A T A C C	CTTAGATCAT; CTTAGATCAT;	A	TTAACTGC GC	TTATACATC 2603_a12.	seq 12.seq
	ATCAAAGACTA	GCCTTAAGCT	CCTTTGATT	GGCGTTTTTT	ATGATAAC Majority	• .
	4860	4870	4880	4890	4900	
4751 4848	ATCAAAGACTA	G C C T T A A G C T : G C C T T A A G C T :	C C T T T G A T T C C T G T G A T T	GCCGTCTTTTC	CATGATAAC 2603_a12.	seq 2.seq
	TACTGCTCCAAC	GCATAATGCTT	FÄAACCAATA	ATTGTGAAAAG	AATTGTAC Majority	
•	4910	4920	4930	4940	4950	
4801 4898	TACTGCTCCAAC	G C A T A A T G C T T G C A T A A T G C T T	T A A A C C A A T A T A A A C C A A T A	ATTGTGAAAAG	AATTGTAC 2603_ai2.s	
	CAATACCACCTO	•	TGTTACTTT	TTTGTTTTGTA	CTTGTTTC Majority	
A951 .	4960	4970	4980	4990	5000	
4948	CRRINCURCCIO	GILIGIGGGA	IMGTTACTT.	TTTGTTTTGA	CACCTUTC 2603_a12.s	seq 2.seq
		TACAGGTTTT1	TGTTATCTG	CGTTGTCAGTT	TTAGCCCC Majority	
4004	-5010	5020	5030	5040	5050	
4901 4998	GUNICITITI	I W.C. V.CEM LEGISL.	TEM THE ATEM T	CGNTGTCAGTT	TTACCACC 2603_at2.s	seq 2.seq
	TTTTCTGTATGA	TGTTTGATTI	ACTTCAAAG	TTTATATTACC	TGCCAATT Wajority	
	5060	5070	5080	5090	5100	
4945 5048	T G T T A T G T A T G A T T T G C T A T A T G A	CCCTTCATT	A C T T C A A A G	TTAATATTACC TTTAGATGACC	T G C C A A C T 2603_ai2.s T G A C A A T G nem316_ai2	seq 2.seq
	TÉGCATAT C C T G	CTGGTGCTTG	TGTTTCTTC	CAGGTTGTAAG	TGCCTTTT Majority	
	5110	5120	5130	5140	5150	•
4995 5098	TAGCAAATCCTG TCGCATAACCTG	CTCCACCAAGCAAG	TGTTTCTTC AGTTTCTTC	AAGGTTGTAAG CANGCTATAAG	TACCUTT 2603_ai2.s	seq 2.seq
			•		TATTTAAT Majority	
	5160	5170	5180	5190	5200	
5045 5148	G C A A G A C C T G T A	ACTTCAAATT	GACCTTGAT	CCTTTGAAGTG	TALGTAAT 2603_a12.s	seq.



	TTTTA	GTGACTT	The frame of the	THE COT C C T C C		TTGTTTC Majority
		5860			•	TGTTTC Majority
·5724	TTTTA		5870	5880	5890	5900
5824	TTTA	ATGACTTT	MATTTCTTGG	TTACCTECACT	AA.CAGGAAGT ACCTTKTTGT	TTTAGTC 2603_ai2.seq TGGTTTA nem316_ai2.seq
	•	5910	5920	5930	•	GGTTTC Majority
5774	AAGTC	TTTACCTC	GTTTCTTACC	A T A THE SIG A A TOTAL	5940	5950 F G G A T T C 2603_ai2.seq
5874	CTTTC	TTCCGTTC	GGTTATTACC	ATAGTCCAATT	TAACATCATI	FGGATTC 2603_a12.seq FGGTTTC nem316_a12.seq
						TGATTT Majority
		5960	5970	· 5980	5990	
5824	TGGAT	TATCAATA	ATTGUTTGACO	MITMACNOTA	C C C W T I T I C C	6000 T C A A T G 2603_a12.seq
5924	TGGAA	C TTCAACA	GTAGTLLAGC (GTTCACCGTA	G C T.G A G T A A G	TGATCT nem316_a12.seq
						AGTCCT Majority
		6010	6020 .	6030	6040	6050
5874	TAAAT	TCAATATC	ACCTGTTTTAC	CTGCTTTTTC	2 4 V T T T P P O O	11000
5974	TGATT	T C.A ATT A T C	TTTETTTTT	CAGCAGUTEC	TACTGUTGCA	AGACCT nem316_ai2.seq
	TTTGC	TTTGAATT	TTAGTGTGAAA	CCTTGGTCAT	CTGTTCTGAG	TTTGTA Majority
		. 6060	. 6070	6080	6090	6100
5924	TCAGC	TGTGAATT	TTAATGTGAAA	CCAUGGICAT	CAATGCTAAG	TTC ATA 2603_a12.seq
6024		EL A AMERICA CAMPAGE	MAGNETICAAA	CCTTGGTCAT	CTGTTATEGAG	TTTGTA nem316_a12.seq
	GTTTG	TATCCTTA	GGAAAATTTTT	TGTATTTCCT	GTTGCTTTAA	G G T T G T Majority
		6110	6i20	6130	6140	6150
5974 6074	GTCTG	TATCCTTA	G C A A A A G T.T T C	TGTAGTTCCT	GAAGCTTAA	G G C T A A 2603_a12.seq
	9111	M AM CICAGO A	G G A A A A I EE I I I	A CLA T	GTTACTTAA	CGTTGT nem316_ai2.seq
	TAGTT	<u>GAACÇCAT</u>	TGTCAAACCTT	TTGTCATTCT	A T C T G T C C A A	ACCAGT Majority
ممم		. 6160	6170	6180	6190	6200
6024 6121	TGTT	GAACCCAT	T G T C A A A C C A T	TIGACATIATA	ATCTGTCCAA	ACCAAG 2603_ai2.seq ACCAGT nem316_ai2.seq
						-
	11111		AGCCTTTGTGA	•	TAACTTTGTA	TTGTTT Majority
6074	TTTT	6210	6220	6230	6240	6250
6165	TTCTT	TABTETS	A A C C T T T G T G A A G C C T T T A A G A	ATTTTTGTT.T.	LAACTT CA TA	A G:G A A C 2603_a12.seq T T C T T T nem316_a12.seq
		6260	6270	6280	•	•
6124	AACTTT		TUAGCAGTAGC		6290	6300
6215	TTTT	ACGMATT	тссстемемс	AATACCTTTGT	CACGTGCAT	AATTAC 2603_ai2.seq nem316_ai2.seq
	CATAAT	гттососс	A G C T G T C A A A A	G T C T A T T T T C C		•
	•	6310	6320	6330	6340	
6174	CATAAT	TTGCGGC				6350 GCT G T C 2603_ai2.seq
6251				ттттсе	TTGTCAGT	ATAATC nem316_ai2.seq
٠,	AAGTTG	TTTGTTT	TTGCAAAGTTT			
		6360	6370	6380	6390	6400
6224	A.A.A.T.C.O	TTTGTTT	GCAAAGTTT	TTATEMATTE	TCCTTTT	7 7 6 4 6 m coss
6272	AAGAT	TTTATC.	TGCAAAGTT	TTATCTACTTG	TGGTTTTET	TTCAGT 2603_a12.seq TTCAGT nem316_a12.seq
		•	TGTGGGCATC			
	•	6,410	6420	6430	6440	6450
6274	GTTCTT	TTGGATAA	TATEGECATE	A B C A A C A A C A C	CATHTE	T. T. J. G. G. J.
6320 :	MITCIT	TTGGATAA	T G T G A G C A.T C	TTTAACAACAC	CTTGHTTGT	TTACCA 2603_ai2.seq TTACCA nem316_ai2.seq
			TTAACTGGAA			
		6460	6470	6480	- 6490	6500
6324	ATGGAA	GAGTGAT	TTAACTEGAA	COCCTTTTC	CACCCACC	1
6370	ATGGCA	GAGTGATI	TTTAACTGGAA	CTGCTTTTGAA	TCAGCCAAG	AMGGAA 2603_a12.seq ATAGAA nem316_a12.seq



Thurs	day, July 29, 2004 6	47 PM	ուս դուս կուս և ուսի այի ո	indicated weight table.	TTTCCAAATATA	
	TTTTTCT	GG A T ALT	TCACTACATT	TETTATATET	TTTCCAAATATA	A A T T Majority
	•	7160	7170	7180	7190	7200
7020	TTTTGAT	GGACATA	TCACTAGATT	TCTTATATCT	TTT00111T1	
7017	TTTTTCT	AGATATA	TCACTAGATT	TCTTATATCT	TTTCCAAATATA	AATT nem316 at2 sec
	· ·				AAATGAAAGATA	G A A T Majority
		7210	7220	7230	7240	7250
7070 7067	CCACCTG	CAATAGA	CATCATAGCT	CCACCTATTA	AAATGAAAGATA	G A A T 2603_a12.seq
••••	CCACCIG	CARIAGA	CAICATAGAT	CCACCTATTA	A A A T G A A A G A T A	GAAT nem316_a12.seq
	TCCTTTC	CCACCTG	TCATCGGAAT	AATTCCTTTT	GGTGGAATATGC	G T C.T Valority
		7260	7270	7280	7290	
7120	TCCTTTC	CCACCTO			GGTGGAATATGC	7300
7117	TCCTTTC	CCACCTG	TCATCGGAAT	AATTCCTTTT	G G T G G A A T A T G C (G T G T. 2603_a12.seq
			•			
	IGGIAAI			CCTCATGATAT	TTCAGAAATCTG	TTTA Majority
:	·	7310	7320	7330	7340	7350
7170 7167	TGGTAAT	TAAATGC	TTGTCACCTT	CCTCATGATA	TTCAGAAATCTG	T T T A 2603_a12.seq
	IUUIAAI	IAARIGU	FIGICACCTT	CCTCATGATA	TTCAGAAATCTG	TTTA nem316_a12.seq
	TTAACAG	CTATTAT	ATTTTTTATC	GATCCTTTAAC	CCACTTCAAAG1	T.A.A. Valority
		7360	7370	7380	7390	7400
7220	TTAACAG	CTATTAT	ATTTTTATC		CCACTTCAAAAG	2
7217	TTAACAG	C.TATTAT	ATTTTHTATC	GATCCTTTAA	C A C T T C A A A A G 1	TTAA 2603_al2.seq
•				•		
	AATIOGI		· ·	•	GCGAAACTGCTT	CTA Majority
4		7410	7420	7430	7440	7450
·7270 · 7267	AATTGGT	TTATTAG	TAATTTTTG	ATAATCCTCCC	GCGAAACTGCTT	ГСТА 2603_ai2.seq
		•	•		GCGAAACTGCTT	<u>-</u>
	TTAACTG	ATATTTG	C C A T C T T T C A	AATCTTTGTAA	GAAATTTTGCC	TTT Majority
	·	7460	7470	7480	7490	7500
7320	TTAACTG	ATATTTG	C·C·A T C·T T T C A	AATCTTTGTAA	GAAATTTTGCC	T.T. 7002 -12
7317	TTAACTG	ATATTTG	CCATCTTTCA	AATCTTTGTAA	GAAATTTTGCC	GTTT nem316_ai2.seq
	TCTCCCG	TCACTAC	T T T G A.A T T A.		T G G T A A A T A A A G	TTT
		7510	7520	7530	7540	
7370	TCTCCCC				TGGTAAATAAAG	7550
7367	TCTCCCG	TCACTAC	TTTTGAATTA		. TGGTAAA,TAAAG TGGTAAATAAAG	TTT 2603_a12.seq
						7
	ATAAICI.			<u> TCAAACGTAG</u>	CTCCTTTGAGAA	G C A Majority
		7560	7570	7580	7590	7600
7420 7417	ATAATCT	TCATTAA	ATTCTTGAAG	TTCAAACGTAG	CTCCTTTGAG'AA	G C A 2603_a12.seq
	WI'WWI'CI	ICALIAA	ATICTTGAAG	TTCAAACGTA.G	CTCCTTTGAGAA	G C A nem316_ai2.seq
	ACTTATT	ATTATCT	TTATCAACTT1	TGTAAATTCA	ATTTCACCTAAC	TTC Majority
·· .		7610	7620	7630	7640	7650
7470	ACTTATT	ATTATCT:	T.T A.T C A A C T.T		ATTTCACCTAAC	
7467	ACTTATT	ATTATCT	TTATCAACTT:	TGTAAATTCA	ATTTCACCTAAC	T T C nem316 at2.seq
		•	•		CACATCACGAAT	
'		7660				TTT Majority
il.	**************************************		7670	7680	7690	7700
7520 7517	TTCTCGT		CGTTATTGTA(GATATTCTCT	CACATCACGAAT CACATCACGAAT	T T T 2603_a12.seq
•	•			· ·		· · · · ·
'	AGGGATT	<u>GAAAAT</u>	T C T A A G T G T A	TTAGGATCCT	CTGATTTAGGAT	T C A Majority
	<u> </u>	7710	7720 .	7730	7740	7750
.7570	AGGGATT	GAAAAT	T C T A.A G T G T	TTAGGAT.CCT	CTGATTAGGAT	T C A 2603 312 sea
7567	AGGGATT	GGKKAAT	CTCTAAGTGT/	TTAGGATCCT	CTGATTTAGGAT	T C A nem316_ai2.seq
			_		<u>C T T A T A A A A C T G</u>	
- •		7760	7770	• •	•	
7620	ATCTTCTT			7780	7790	7800
	ATGTTGTT	CTACCAT	L L A G I G T C A T A F T A G T G T C A T A	GAATTTGTTA	CTTATAAAACTG CTTATAAAACTG	T C A 2603_a12.seq
						■ U A HUMBID BIZ.Sed

	T C T A COST SOUSDINGOLA A	2) a lengtion, ettler licilies ender	their than their That went			·
	TCTA GENERAL	CATE AT KIT G'T	CAGTCTTAC	TTTTTGTCCT	TCTCCTAAGT	T Majority
	7810	78	20 7	7830	7840 . 78	350
7670	TCTAGTTTCAC	CATCATATCT	CACTCTTAC		TCTCCTAAAT	
7667	TCTAGTTTCAC			TTTTTCTCC	T C T C C T A A A T	T 2603_ai2.seq
			ond id I I i c		I CHECCIAAGI	T nem316_al2.seq
	CAAACCTCTAA	CGTAGAGTT	TATTTTCA	TGTATTCTAA	TTTAACCCCT	T. Made to
	7860	•				I Majority
						30 <u>0</u>
7720	CAAACCTCTAA	A CENTAGAGTI	TATTTEGA	TGTATTCTAA	TTTAACCCCC	T 2603 at2 sea
7717	CAAACCTCTAA	A C G T A G A G T T	TATTTTGA	TGTATTCTAA	TTTAACCCCT	T nem316 al2.seg
					•	-
	TARGIATICCA	CCATCATTA	TTAGGCCCA	CCAGTTGCAA	TGCTATCTTT	C_ Majority
	7910	792	20 7	930 -	7940 79)50
7770	TAAGTATTCCA	CCATCATTA	TTACCCCCA	•		. .
7767	TAAGTATTCC	CCATCATTA	TTACCCCCA	CCACTTCCAA	TECTATOTT	C 2603_ai2.seq
			irradocer	CCAGIIGCAA	ICCIALCITY	U nem316_ai2.seq
	ATTATACTTCC	CATCATTTCC	CTGTAAAGT	ATAATCACTT	CCTTCTAATC	r Wolanieu
	7960	-		.•		r Majority
						00
7820	ATTAMACTTCC	CATCATTTCC	CTGTAAAGT	ATAATCACTT	GGTTGTAATG	[2603 ai2.seg
7817	ATTATACTTCC	CATCATTTCC	CTGTAAAGT	ATAATCACTT	G G T T G T A A T G	nem316_a12.seq
						-
	TTGTCCGTTGC	CAAGUTGTA	AATTGATTT	TGTCACCCAT	AGGATCTTCTA	Majority
	8010	· 802	8 0	030 8	8040 80	50
7870	TTGTCCATTAC	CAAGCTGTA	A A T T C A T T T			
7867	TTGTCCGTTGC	CAAGCTGTA	AATTCATT	TOTOLOGICAT	AGGATCTTC	2603_a12.seq
			KALIGALIL	IGICACCCAE	AGGATETTETA	nem316_ai2.seq
	TAGTTCCATTA	ACAATTGAG	TTTTCTTT	GTTAA'AATĊT	TTTC	. Walaaisaa
	8060				•	_ najority
•		807	-		090 81	
7920	TAGTTCCATTA	ACAATTGAG	TTTTCTTTT.	GTT A.A A A T C G	TTTCAAATTGT	2603.at2.sea
7917.	TAGTTCCATTA	ACAATTGAG	TTTTCTTTT	GTTAAAACCT	TTTCAAATTGT	nem316 at2 sec
				• • • • • • • • • • • • • • • • • • • •		•
	TGCTGAATTTT	AGATAAAAT	TTCATTGTT	A G A T G T A T C G	<u>GCTGAAGTTAC</u>	Majority
٠.	. 8110	. 812	o8:	130 8	140 . 81	50
7970	TGCTGAATTTT	AGATAAAAT	TTCATTCTT			
7967	TGCTGAATTTT	AGATAAAAT	TTCATTGTT	A G'A T G A A T C C	G A CTTAC	2603_ai2.seq
		• .				•
	TATCGGGGTGT	AGTACTCAG	GTTTGGAAG.	AGAATGACTT	CATTAGTTCTC	Valority
	8160	817		·		
enża					190 820	00
8020 8017	GATAGGGGTGT	AGTACTCAG	GTTTGGAAG.	A G A A G G A C G T	CATTAGTTCTG	2603_ai2.seq
	TATCGGGGTAT	AMILAUICAG	GITTEL GAAG	A G A A T G'A C T T	CATTAGTTCTG	nem316_ai2.seq
	TTATTTCTCCA	TCTCAAAGT	TT	TCCTCTTT0.		
		1	A I K A A K G C I	I CCICILICA	ALLILIGAAAA	Majority
•	8210	822			240 829	
8070	TEATTTCTCCA	TCTGAAAGT	TTAAAAGC.T	TCCTCTTTCA	ATTTTCAAAA	2603 242 622
8067	TTATTTCCCCA	TCTGAAAGT	TAAAAGCT	TCCTCTTTCA	ATTTTTGAAAA	nem316 at2 sea
	•					
	GTACCATCTTG	A.TTTT.TCTT	A TIACTCCTC	ATTATAAACT.	TGTCTAAAAGC	Majority
	8260	8270		• • •	290 830	
ei 20	GTACCATETTC					
R117	. OTACCAICILG	A 1"	ATACTECTE	A F T A T A A A C T	TGTCTAAAACC	2603_a12.seq
	·C T A C C A T C T T C		A I A MIT C C'I C. I	A TTATAAACT'	T.C. T.C. T. A.	Clai 310
	GTACCATCTTG	ATTITUTE	· · · · · · · · · · · · · · · · · · ·		IOICIARRAGO	newsto_arz.seq
	GIRCCRICILG			• •		
	AGATATATETA	TACCAAAAT	TAAAGATGT	• •		
	-A G A T A T A T C T A	T A C C A A A A T 8320	T A A G A T G T (30 88	C T C T T T A A A C	Hajority
3170	-A G A T A T A T C T A 8310 -A G A T A T A T C G A	T A C C A A A A T 8320	F A A A G A T G T (83	30 83 CATAATTTT	CT CTTTT A A A C	Najority
3170 3167	-A G A T A T A T C T A 8310 -A G A T A T A T C G A	T A C C A A A A T 8320	F A A A G A T G T (83	30 83 CATAATTTT	CT CTTTT A A A C	Najority
8170 8167	-A G A T A T A T C T A 8310 A G A T A T A T C T A A G A T A T A T C T A	T A C C A A A A T 8320 T A C C A A A A T T A C C A A A A T	T A A A G A T G T () 83 T A A A A A T G T (T A A A G A T G T (30 83 CATAATTTTT CATAATTTTT	C T C T T T T A A A C 40 835 C T C T T T T A A A C C T G T T T T A A A C	Majority 0 2603_a12.seq nem316_a12.seq
3170 3167	-A G A T A T A T C T A 8310 A G A T A T A T C T A A G A T A T A T C T A	T A C C A A A A T 8320 T A C C A A A A T T A C C A A A A T	T A A A G A T G T () 83 T A A A A A T G T (T A A A G A T G T (30 83 CATAATTTTT CATAATTTTT	C T C T T T T A A A C 40 835 C T C T T T T A A A C C T G T T T T A A A C	Majority 0 2603_a12.seq nem316_a12.seq
3170 3167	A G A T A T A T C T A 8310 A G A T A T A T C T A A G A T A T A T C T A T A T T T A T A T A A	T A C C A A A A T 8320 T A C C A A A A T T A C C A A A A T A G T T T G G T T	F A A A G A T G T (83 F A A A A A A T G T G F A A A G A T G T G C G T G T T C C A 1	ATAATTTT 30 83 CATAATTTTT CATAATTTTT CATACTTTTA	CTGTTTTAAAC CTGTTTTAAAC CTGTTTTAAAC	Najority 0 2603_al2.seq nem316_al2.seq Najority
	A G A T A T A T C T A 8310 A G A T A T A T C T A A G A T A T A T C T A T A T T T A T A T A A 8360	T A C C A A A A T 8320 T A C C A A A A T T A C C A A A A T A G T T T G G T T 8370	F A A A G A T G T G 83 F A A A A A A T G T G F A A A G A T G T G 6 G T G T T C C A 7	ATAATTTTT 30 83 CATAATTTTT CATAATTTTT GTTCTTTTA 80 83	C T C T T T T A A A C 46 835 C T G T T T T A A A C C T G T T T T A A A C C T G T T T T A A A C	Majority 0 2603_al2.seq nem316_al2.seq Majority 0
3220	A G A T A T A T C T A 8310 A G A T A T A T C T A A G A T A T A T C T A T A T T T A T A T A A 8360 T A T T T A T A T A A	T A C C A A A A T 8320 T A C C A A A A T T A C C A A A A T A G T T T G G T T A G T T T G G T T	F A A A G A T G T G 83 F A A A A A A T G T G F A A A G A T G T G 6 G T G T T C C A 7	30 88 CATAATTTT CATAATTTT CATAATTTT CATAATTTT CGTTCTTTTA 80 83	C T C T T T T A A A C 40 835 C T G T T T T A A A C C T G T T T T A A A C C T G T T T T A A A C	Majority 0 2603_al2.seq nem316_al2.seq Majority 0
	A G A T A T A T C T A 8310 A G A T A T A T C T A A G A T A T A T C T A T A T T T A T A T A A 8360	T A C C A A A A T 8320 T A C C A A A A T T A C C A A A A T A G T T T G G T T A G T T T G G T T	F A A A G A T G T G 83 F A A A A A A T G T G F A A A G A T G T G 6 G T G T T C C A 7	30 88 CATAATTTT CATAATTTT CATAATTTT CATAATTTT CGTTCTTTTA 80 83	C T C T T T T A A A C 40 835 C T G T T T T A A A C C T G T T T T A A A C C T G T T T T A A A C	Majority 0 2603_al2.seq nem316_al2.seq Majority 0
3220 3217	A G A T A T A T C T A 8310 A G A T A T A T C G A A G A T A T A T C T A T A T T T A T A T A A 8360 T A T T T A T A T A A T A T T T A T A	T A C C A A A A T 8320 T A C C A A A A T T A C C A A A A T A G T T T G G T T A G T T T G G T T A G T T T G G T T	F A A A G A T G T (83 F A A A A A T G T (F A A A G A T G T (6 G T G T T C C A 1 83 C G T G T T C C A 1	CATAATTTTT CATAATTTTT CATAATTTTT CATAATTTTT GTTCTTTTA 80 83 CGTTCTTTTA CGTTCTTTTA	C T C T T T T A A A C 46 835 C T G T T T T A A A C C T G T T T T A A A C C T G T T T T A A A C C T G T C C A T T T 50 840 C T G G T C C A T T T C T G G T C C A T T T	Majority 0 2603_ai2.seq nem316_ai2.seq Majority 0 2603_ai2.seq nem316_ai2.seq
3220 3217	A G A T A T A T C T A 8310 A G A T A T A T C T A A G A T A T A T C T A T A T T T A T A T A A 8360 T A T T T A T A T A A A T A T T T A T A	T A C C A A A A T 8320 T A C C A A A A T T A C C A A A A T A G T T T G G T T A G T T T G G T T A G T T T G G T T A C C T T T A G G	F A A A G A T G T (83 F A A A A A T G T G F A A A G A T G T G 83 G G T G T T C C A T G G T G T T C C A T G G T G T T C C A T	CATAATTTTT CATAATTTTT CATAATTTTT CATAATTTTT GTTCTTTTA 80 83 CGTTCTTTTA CGTTCTTTTA	C T C T T T T A A A C 46 835 C T G T T T T A A A C C T G T T T T A A A C C T G T T T T A A A C C T G T C C A T T T 50 840 C T G G T C C A T T T C T G G T C C A T T T	Majority 0 2603_ai2.seq nem316_ai2.seq Majority 0 2603_ai2.seq nem316_ai2.seq
3220 3217	A G A T A T A T C T A 8310 A G A T A T A T C G A A G A T A T A T C T A T A T T T A T A T A A 8360 T A T T T A T A T A A T A T T T A T A	T A C C A A A A T 8320 T A C C A A A A T T A C C A A A A T A G T T T G G T T A G T T T G G T T A G T T T G G T T	F A A A G A T G T G 83 F A A A A A A T G T G F A A A G A T G T G 83 G G T G T T C C A T G G T G T T C C A T G G T G T T C C A T	CATAATTTTT CATAATTTTT CATAATTTTT CATAATTTTT GTTCTTTTA 80 83 CGTTCTTTTA CGTTCTTTTA	C T C T T T T A A A C 46 835 C T G T T T T A A A C C T G T T T T A A A C C T G G T C C A T T T 90 840 C T G G T C C A T T T C T G G T C C A T T T	Majority 2603_al2.seq nem316_al2.seq Majority 2603_al2.seq nem316_al2.seq Majority
3220 3217	A G A T A T A T C T A 8310 A G A T A T A T C T A A G A T A T A T C T A T A T T T A T A T A A 8360 T A T T T A T A T A A A T A T T T A T A	T A C C A A A A T 8320 T A C C A A A A T T A C C A A A A T A G T T T G G T T A G T T T G G T T A G T T T G G T T A C C T T T A G G 8420 A C C T T T A G G	TAAAGATGTO 83 TAAAAAATGTO TAAAGATGTO AAAGATGTO 83 GGTGTTCCAT	30 83 CATAATTTTT CATAATTTTT CATAATTTTT GGTTCTTTTA 80 83 CGTTCTTTTA GGTTCTTTTA GTTCTTTTA GTTCTTTTA GTTCTTTTA	C T C T T T T A A A C 46 835 C T G T T T T A A A C C T G T T T T A A A C C T G T T T T A A A C C T G G T C C A T T T C T G G T C C A T T T C T G G T C C A T T T A A A T A A T G A A G 40 845	Majority 2603_ai2.seq nem316_ai2.seq Majority 2603_ai2.seq nem316_ai2.seq Majority

Alignment Report of WO 2006/078318

Alignment Report of WO 2006/078318 Thursday, July 29, 2004 6:47 PM 8460 8470 8480 8490 8500 TTTTTGTAAGTTTCCAGAGATTATCTGTGTTTGATAACTATCTAAGGGAA 2603_a12.seq 8320 TTTTTGTAAGTTTCCAGAGATTATCTGTGTTTGATAACTATCTAAGGGAA nem316_a12.seq ACAAAAGTAACTCCCCATTTCCTTTTATATCCTCGGGCTTATCAGTA Majority 8520 8530 8540 ACAAAAGTAACTCTCCCCATTTCCTTTTATATCCTCGGGCTT.ATCAGTA 2603_ai2.seq 8370 ACAAAAGTAACTCTCCCCATTTCCTTTTATATCCTCGGGCTTATCAGTA nem316_a12.seq 8367 AGTAGAAATTACTTTATTTAGATATCCATTTTTTTCATTTGTTCAAA Najority 8560 . 8570 8580 8590 8600 AGTAGAAATTACTTTTATTTAGATATCCATTTTTTTTCATTTGTTCAAA 2603_ai2.seq 8420 A GTAGAAAATTACTTTTATTTAGATATCCATTTTTTTTCATTTGTTCAAA nem316_ai2.seq 8417 TTGGCTTTCATATGATGCACCCAGTTTAAAATTATTAATAGCATATGATC Najority 8610 8620 8630 8640 8650 TTGGCTTTCATATGATGCACCCAGTTTAAAATTATTAATAGCATATGATC 2603_ai2.seq 8470 TTGGCTTTCATATGATGCACCCAATTTTAAAATTATTAATGCATATGATC nem316_a12.seq 8467 TTGTTGGAACACCATCAGTTATATGAACAATAATTTTTTGACTATTTCGA Majority 0338 8670 8690 8700 8520 TCGTAGGAACACCATCAGTTALATGAACAATAATTTTTTGACTATTTCGA 2603_a12.seq TTGTTGGAACACCATCAGTTATATGAACAATAATTTTTTGACTATTTCGA nem316_a12.seq 8517 TTTACTTGACTCAAAATATCATCTGCCTCCATGAAGGCTTTCATAGTAAA Majority 8710 8720 8730 8740 . 8750 TTTACTTGACTCAAAATATCATCTGCCTCCATGAAGGCTTTCATAGTAAA 2603_ai2.seq TETACTTGACTCAAAATATCATCTGCCTCCATGAAGGCTTTCATAGTAAA nem316_a12.seq T G T T T C T C C T A C T T T A C T A A C A T A C T A C T G C T T T T G T T G C T C T G G A G T T A Majority 8770 8780. - -8800 8790 TGTTTCTCCTACTTTACTAAGATACTACTCTTTTTTTTTCTTCCTCTGGACTTA 2603_a12.seq TGTTTCTCCTACTTACTAAGATAGTACTGCTTTTGTTGCTCTGGAGTMA nem316_a12.seq GTCCGTTTGTAGTTGATCCCCATTTAGCTTTAGGAGCTTCTGTCGGAATC Majority 8820 8810 8830 8840 8850 ATCCATTGGTAGTAGATCCCCACTTAGCTTTAGGAGCTTCTGTCGGAATC 2603_ai2.seq GTCCGTTTGTAGTTGATCCCCATTTAGCTTTAGGAGCTTCTGTAGGAATC nem316_ai2.seq CTTTTTATAATCTCTTCAGCATTATTTGTTAATTGTTTATGACTATAATT 8880 - . 8890 . 8900 CTTTTTATAATCTCTTCAGCATTATTTGTTAATTGTTTATGACTATAATT 2603_a12.seq CTCTGTCTGAATTGTGAACTTAGTTTGAAGGCCATAATATTTATCATCTT Majority 8910 8920 · 8930 8940. 8950 CTCTGTCTGAATTGTGAACTTAGTTTGAAGGCCATAATATTTATCATCTT 2603_a12.seq 8770 CTCTGTCTGAATTGTGAACTTAGTTTGAAGGCCATAATATTTATCATCTT nem316 ai2.seq 8767 CTTTAAATCCTTTTACGACATCTACACTCCTACCATCAAAAATATCTGAA Hajority 8960 8980 8970 8990 9000 CTTTAAATCETTTTACGACATCTACACTCCTACCATCAAAAATATCTGAA 2603_ai2.seq 8820 CTTTAAATCCTTTTACGACATCTACACTCCTACCATCAAAAATATCTGAA nem316_ai2.seq 8817 CCATAGGTAACTAATGCAACCCTATTATCACTGTTTGCTCCTAAAATATC Hajority 9010 9020 9030 9040 9050 8870 CCATAGGTAACTAATGCAACCCTATTATCACTGTTTGCTCCTAAAATATC 2603.ai2.seq CCATAGGTAACTAATCCAACCCTATTATCACTGTTTGCTCCTAAAATATC nem316_a12.seq TTTTACTGCGCTCCCAAGAGCTTCGGCAGCTTTCTTGGCTTTATTATGCC Majority 9060 9070 9080 9090 TTTTACTGCGGTCCCAAGAGCTTCGGCAGCTTTCTTGGCTTTATTATGCC 2603_ai2.seq

TTTTACTGCGGTCCCAAGAGCTTCGGCAGCTTTCTTGGCTTTATTATGCC nem316_ai2.seq

8920

8917

Aligna Thurs	nent Report of Aragan day, July 29, 2004, 6:4	2000/0 /0310 greener, usag J. nein me 7 RM	thod with Weighted residue	weight table.		FC1/US200.
	TTTGAAA	A TTT G G G C C			ATTATCGAGTA	C C Votoste
		9110	9120	9130	9140	9150
8970 8967	TTTGAAA	A TTTGGGCCA A TTTGGGCCA	T C G T T A T T C A	T T G A G T T A G A T T G A G T T A G A	ATTATCGAGTA ATTATCGAGTA	
					TTACTATGGTT	T T Majority
9020	AAGACAA	CATCTAACGG	CTTTTCTTTC	TCCACTCCTT	9190 TTACTATGGTT	9200 T. T. 3603 -13
9017	o o . c . c	CAICIAACGG	CILILGITTE	TCCACTGGTT	TTACTATGGTT	TT nem316_a12.seq
	TOCKCIGA	9210	9220	9230	GCTAAATCACC	•
9070 9067	TCCACTGA	A C A G T T A A.C T	CAATTTTATA	TTTATTATCA	9240 G C T A A A T C A C C G C T A A A T C A C C	9250 T A 2603_ai2.seq
					TTCTCTTATAT	-
		9260	9270	9280	9290	G C Majority 9300
9120	CTT.CTGAA	ATACGTTTA	GATAATGTTC	CCTCTCCAAT	TTCTCTTATATA	
9117	· ·	, KIKUUIIIK	GAIAAIGTTC	CCTCT-GGAAT	TTCTCTTATAT	G C nem316_ai2.seq
	··	9310	TGGGTTAACT 9320	9330		
9170	TCACCTTC	t			9340 CTGACTTTCCA	9350
9167	TORCCLIC	ACTIGAATA	I G.G G T T A A C T	G C T T T T G C C T	CTGACTTTCCA	TT nem316_ai2.seq
	TOURNETO	9360	9370	9380	T C C T T T G T A T C 1	
9220	TGGAACTG	AACCTTTAA	CATGCTCAAG	TTTATACAT	TCCTTTCTATCT	9400
9217	IGGAACIG	AACCIIIAA	CATGCTCAAG	TTTATAAGAT	TCCTTTGTATCT	T T mem316_a12.seq
	CATAAATT	9410	<u> 9420 .</u>	•	T T C G T G A T T T T C	47
9270	CATAAATT	CCTGTGGGG	GGATACTCCT	9430 TATCTAGTTC	TTC TTC ATTT	9450
9267	CATAAATT	CCIGIGGG	GGATACTGCT	TATCTAGTTC	TTCGTGATTTT(T nem316_ai2.seq
1	<u> </u>	9460	9470	9480	TAGTTTTTCCAT	• •
9320 9317	C C A.A T T G T	GGAATTTTT	A T C A C C A C T A A T C A C C A C T A	TTTTCTATCC	FACTTTTCCAT	9500 T 2603_a12.seq
	•			•		
	MOLOTOKA	9510	9520	9530	TATAACCTTCG 9540	
370	ACTCTCAA	CCTTAACTT	GCCAAGTCTG	G T T A G T C T T T T	CTATAACCTTCC	9550
9367	ROICICAA	CCITAACIT	GCCAAGTCTG	GTTAGTCTT1	TATAACCTTCG	G nem316_a12.seq
	<u>GCGCIGII</u>	9560	9570		AGATTATCAAA	
9420	GCGCTGTT	TCTTCTGAT	AAAGTATAATA	9580 (1 4 C 4 T T 4 T O 4 4 4	9600
417	CCCCTCTT	TCTTCTCAT	AAGIAFAAT	CICCAGGTATE	A G A T T A T C A A A	A nem316_ai2.seq
			TCAGCAGTTA	CTTTTTCTAT	TTTACTTTTTG	.G Wajority
ina		9610	9620	9630		650
)470)467.	GTAGCTTC	A C C T G T T A G (CTCAGCAGTT CTCAGCAGTT	CTTTTTCTAT CTTTTTCTAT	TTTACTTCTC	G 2603_a12.seq G nem316_a12.seq
	ATGAGCAG	TAGTTTTAA	AAC:AAAGGTA	GCTTTTGAAA	GTGGTTTGTTC	T Majority
		9660	9670	9680	9690 9	700
9520 9517	ATGAGCAG ATGAGCAG	T A G T T T T T A A T A G T T T T T A A	AACAAAGGTA AACAAAGGTA	A G C T T T T G A A A A G C T T T T G A A A	GTGGTTTGTTC GTGGTTTGTTC	T 2603_a12.seq T nem316_a12.seq
-	GGTCATCT	GTCTTTTAA	CAACTAACTI	TCCTTTAGCA	CCATTTTCCGG	T Kajority
٠.		9710	9720	9730	9740 9	750
1570		· · · · · · · · · · · · · · · · · · ·				
9570 9567	GGTCATCT	G T C T T T T T A A G T C T T T T T A A	1	TTCCTTTAGCA TTCCTTTAGCA	C C A T T T T C C G G	T 2603_a12.seq

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10917	7 C T	CMC	C C C T A	TCATO	ATGAGT	TGGT	AAAAGT	TGCTA	TCTTT	TTTTCC	C A 2603_a12.seq
				·CAI	ALLGAGI	TGGT	AAAAGT	TGCTA	TCATTT	TTTCC	G A 2603_ai2.seq G A nem316_ai2.se
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			1111	10	11120			OIGAA		ICALLI	CC Majority
10967	AC	TTT					.11130	· .	11140		11150
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								CIGAA	ACARII	ICATTT	C C nem316_a12.sec
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11017	TTO	ATG	GAAC	TATCA	TAGACA	TGAT					11200 G A 2603_a12.seq
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11067	TAA	TTA	CAAA	TTGGT	TAAGTA	AAATT	GGAGA	TACA	CGTTTA	AMGAAC	
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	CAT	TTT	CTTC.	гсстт	TGTGCT	С A T C T					
			11260	n ·	11270	OKICI		AATT		ATCAT	A T Majority
11117	CAT	TTT			11270		11280		11290		11300
11117	CAT	TTT	CTTC	ICCTT FCCTT	TGTACT	CATCI	AGARAC	AATU	ATCAAAA	ATCAT	11300 A T 2603_a12.seq
٠.	-				•				ryonnan	A A C A	A I nem316_a12.seq
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11167	TCC	TCC	GATAC	AGAT	AGCCGT	ACTAA	0.00	10777			11350 A A 2603_a12.seq
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CTAGAAACTGTTCATAGATAGCTCCAAACAAATATATTATACACCCCTCT measures.	12217	TTCTCTT	GGATACCGCA	TAAAAATCTG	GACGATAATC	TTAACACCC	
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Decoration 'Decoration #1': Shade (with solid black) residues that differ from the Consensus.

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701	TGTGCAAAAGTG	CACCCTCCTAC	CAACTCTTCC	ATCTCTCTT	
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851	GTATCACAATTTT	AACTAAAATAACC	TCACTACTAC	AATAAKACTA	A A A A
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951 1001 1001 1051 1051 1101 1151 1201	A C C A A T C C T T G G A T A C C A A T C C T T G G C T G C A A T A T A A A A C C C T A C A A T A T	FAAAAA GATATA C FAAAAA GATATA C FAAAAA GATATA C 1020 CAGCTAAAAA CATC CAGCTAAAAA CATC CAGCTAAAAA CATC CAGCTAAAAA CATC CAATTAAAAAAAA CAATTAAAAAAAA ATACTCTTAAGGCA 1120 ATACTCTTAGGCA T170 CATAAATGTTCC CATAAATGTTCC CATAAATGTTCC CATAAATGTTCC CATAAATGTTCC CATAAATGTTCC CATAAATGGTTCC CATAAATGGTTCC CATAAATGGTTCC CATAAATGGTTCC CATAAATGGTTCC CATAAATGGTTCC CATAAATGGTTCC CATAAATGGTTCCC CATAAATTGTTCCCC	G C A G T T A G A T G C A G T T A G A T G T C G G A A A A 1030 G T C G G A A A A A G T C G G A A A A G T C G G A A A A C A G C A A A C C 1080 G A G C A A A C C G A G C A A A C C T A T A G T A C T 1130 A T C G A G T A C T A T C G A G T C C 1180 A T C G A G T C C 1230 T A A A G T T C G T A A A G T T C G T A A A G T T C G T A A A G T T C G T A A A G T T C G T A A A G T T C G T A A A G T T C G T A A A G T T C G T A A A G T T C G T A A A G T T C G T A A A G T T C G T A A A G T T C G T A A A G T T C G T A A A G T T C G T A C C A C A C A	T C A A A A T A C C C T C A A A A T A C C C T A C C C C	A T A A cohl_al2.seq A T A A a909_al2.seq A T A A a909_al2.seq C G T A Majority 1050 C G T A cohl_al2.seq C G T A a909_al2.seq T G G C Majority 1100 T G G C cohl_al2.seq T G G C a909_al2.seq T A T A Majority 1150 A T A cohl_al2.seq A T A a909_al2.seq C G A Majority 1200 C C A a909_al2.seq C G A a909_al2.seq C G A A cohl_al2.seq C G A a909_al2.seq C G A Majority 1250 C G A A cohl_al2.seq C A A cohl_al2.seq C A A goon_al2.seq C A A soon_al2.seq C A A cohl_al2.seq C A A cohl_al2.seq C A A Majority 1250 C A A cohl_al2.seq
1001 1001 1051 1051 1101 1101 1151 1201	A C C A A T C C T T G G A T A C C A A T C C T T G G C T G C A A T A T A A A A C C C T A C A A T A T	FAAAAA GATATA CATA CAAAAAAAAAAAAAAAAAAAAA	C C A G T T A G A T G C A G T T A G A T G T C G G A A A A 1030 C G T C G G A A A A A G T C G G A A A A G T C G G A A A A C C A G C A A A C C 1080 C A G C A A A C C G A G C A A A C C T A T A G T A C T 1130 T A T A G T A C T A T C G A G T C C 1180 A T C G A G T C C 1230 T A A A G T T C G T A A A G T T C G T A A A G T T C G T A A A G T T C G T A A A G T T C G T A A A G T T C G T A C C A C A C A 1280 T A C C A C A C A C A	T C A A A A T A C C C T C A A A A T A C C C T A C C C C	ATAA cohl_al2.seq ATAA a909_al2.seq ATAA a909_al2.seq ATAA a909_al2.seq GTA cohl_al2.seq GTA a909_al2.seq TGGC Majority 1100 TGGC Cohl_al2.seq TGGC a909_al2.seq ATA Majority 1150 ATA cohl_al2.seq ATA a909_al2.seq CGA Wajority 1200 CGA cohl_al2.seq CGA cohl_al2.seq CGA cohl_al2.seq CGA cohl_al2.seq CGA cohl_al2.seq CGA a909_al2.seq CGA Majority 1250 CGA A cohl_al2.seq CGA Majority 1250 CGA A cohl_al2.seq CGA A Majority 1250 CGA A cohl_al2.seq

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Alignr Thurs	nent Report of WO 2006/078318 in r day, July 29, 2004 ocas rm	method with Weighted residue weight table.	PCT/US20
		GA G GA TA CICA CAT T C T T A A G G T A A C A G A A	A G T G A C Majority
	1310	1320 1330 1340	1350
1301 1301	G C G A T A A A T C T A G C T T G C G A T A A A T C T A G C T T	T G A G G A T A C C A C T T C T T A A G G T A A C A G A A T G A G G A T A C C A C T T C T T A A G G T A A C A G A A	A G T G A C cohl_ai2.seq
•		GCTÀTCTGGCTTACAGTATTACCAACCA	<u>-</u>
	1360	1370 1380 1390	1400
1351 1351	G C T C A T A A T C G C A A T A G C T C A T A A T C G C A A T A	G C T A T C T G G C T T A C A G T A T T A C C A A C C A G C T A T C T G G C T T A C A G T A T T A C C A A C C A	CAGTGA cohl_ai2.sèq
	1	<u>T G T A G A A A G A T T T G G C A A C T G T C C T C T A</u>	
	1410	1420 1430 1440	1450
1401 1401	TTAACTTAAAAATCT	T G T A G A A A G A T T T G G C A A C T G T C C T C T A	ACACTT cohi ola con
.1401		TGTAGAAAGATTTGGCAACTGTCCTCTA	
	1460	C A A A T G C G A T T A C A G T G T C G G G C C A A T A 1470 1480 1490	TTTGAT Majority
1451	TCTTGAATAGTTTGGT	CAAATGCGATTACAGTGTCGGGCCAATA	TTTCAT cohi at2 coa
1451	1 C I I G A A T A G T T T G G T	CAAATGCGATTACAGTGTCGGGCCAATA	TTTGAT a909_a12.seq
:	•	A A A A A A A G A T A A T A G C A A T A A A T G C T T	GAATAA Majority
1501	GACCAATCCTAAACTC	1520 1530 1540 A A A A A T A A G A T A A T A G C A A T A A A T G C T T	1550
1501	GACCAATCCTAAACTG	AAAAATAAGATAATAGCAATAAATGCTT	GAATAA cont_at2.seq GAATAA a909_at2.seq
٠.	GTTTACTATTTTGACG	A G A T A A C A T T A G T C T T T T T A T A T C T T T C	TAATAT Majority
.1551	1560	1570 1580 1590	1600
1551	GTTTACTATTTTGACG	A G A T A A C A T T A G T C T T T T T A T A T C T T T C A G A T A A C A T T A G T C T T T T T T A T A T C T T T C	TAATAT cohl_ai2.seq TAATAT a909_ai2.seq
	TGGCAAACAAGCCACG	T A A G T T A G A T A G A A A A C A A T C G A A A T T A	A A A T T C Majority
	1610	1620 1630 1640	1650
1601 ,1601	T G G C A A A C A A G C C A C G T G G C A A A C A A G C C A C G	T A A G T T A G A T A G A A A A C A A T C G A A A T T A T A A G T T A G A T A G A A A A C A A T C G A A A T T A	A A A T T C cohl_ai2.seq A A A T T C a909 ai2.seq
· •• .		T G G A A T A A C C A T T G T T A A A A G G T A A T T G	
•	1660	1670 1680 1690	1700
1651 · -1651	C C T C A A C G A T A T T A A A	T G G A A T A A C C A T T G T T A A A A G G T A A T T G T G G A A T A A C C A T T G T T A A A A G G T A A T T G	C C T A C A cohl_ai2.seq
		T A T C A A A G T T A G C A A A T A T A G C A T A C A A	
	1710 .	1720 1730 1740	1750
1701 1701	C C A A T A A A T G T T C T G A C C A A T A A A T G T T C T G A	T A T C A A A G T T A G C A A A T A T A G C A T A C A A T A T C A A A G T T A G C A A A T A T A G C A T A C A A	A G G A A T cohl_ai2.seq
		A G A G C T A C C A T A G A T A C A G T C A A G C T A A	
	1760	'1770 1780 1790	1800
1751	CGCAAAGACATAGTTG	A G A O C.T A C C A T A G A T A C A G T C A A G C T A A	CTCTAC cobi at 2 con
1751		A G A G C T A C C A T A G A T A C A G T C A A G C T A A	
	1810	1820 1830 1840	· · · · · · · · · · · · · · · · · · ·
1801 ·	CAAATAAACTAGCTTT	AATAAAATCTTTTGCACTCTCTCTATTT	T T.C.C.A.G. cobl. at 2 sec.
1801	CAAATAAACTAGCTTT	AATAAATCTTTTCCACTCTCTCTATTT	T T C C A G a909_a12.seq.
:		C T A A A A A T A G A G C T A G A G C A A C C A T A T T	CATCGG Majority
1851	AAATAGCGAAACTTG	1870 1880 1890 C T A A A A A A T A G A G C T A G A G C A A C C A T A T T	1900
1851	AAAAAGCGAAACTTG	C T A A A A A T A G A G C T A G A G C A A C C A T A T T	CATCGG a909_a12.seq
	TAAACCGATAAAGGTTT	T C T C G A C C A C G A T T A G C A A G T A T A A C T T	TTAAAA Majority
1001	1910	1920 1930 1940	1950
1901 1901	TAAACCGATAAAGGTT	T C T G G A C C A C G A T T A G C A A G T A T A A C T T T C T G G A C C A C G A T T A G C A A G T A T A A C T T	TTAAAA cohl_ai2.seq TTAAAA a909 ai2.seq

Thurs	day, July 29, 2W U								_	PC1/US200
•	GTGATCT	TAPA T	A A G A G T	A C.A.C.C.A	T'A "AI GE	TGATT	TCAAA	TCAAAT	AAAATA	Majority
	jj 14.1	1960	Hard tarrill Healt seem	1970	tteere erreri el	1980		1990 .	200	•
1951	GTGATCT	TAAT	AAGAGT	ACACCA	TAAC	TTGATT	TCAAA			
1951	GTGATCT	TAAT	AAGAGT	ACACCA	TAAC	TTGATT	T C A A-A	TCAAAT	AAAATA	agng at 2 seg
	AAAGCAA		ATCGG	<u>A A Ç G A T</u>	TGAAA	AATCA	ACCTT	TAAAAA	TTCTGC	Majority
	•	2010		2020		2030		2040	2050	
2001	AAAGCAA	CTAA	CATCGG.	AAGGAT	TGAA	AAATCA	ACCTT	TAAAAA	TTCTGC	cobi al2 sea
2001	AAAGC'AA	CTAA	CATCGG	AAGGAI	TGAA	AAATCA	ACCTT	TAAAAA	TTCTGC	a909_a12.seq
_	TCCTGGT	ATTA	ATGGAA:	4 T C 4 A A	CCATO	ATCLA	T 4 C 4 4	4 4 0 4 4		
:		2060			CCAIC	•	IACAA	•	AGGCAG	Majority
				2070		2080		2090	2100	
2051	TCCTGGT	ATTA	ATGGAA	A T G A. A A	CCATO	CATCAA	TACAA	AAGATA	AGGCAG	cohl_at2.seq
LOGE	TCCTGGT	ALIA	CIGGRA	AIGAAA	CCAT	CATCAA	TACAA	AAGATA	AGGCAG	a909_a12.seq
	AAAGAAT	GGCGA	TTGTC	A'C CATT	TTACE	TGTAT	TTGTC		AAATTC	Majority
•		2110	-	2120		2130	• •	2140	2150	
2101	AAAGAAT	GCCG	TTGTC		TTACC		T T C T C			
2101	AAAGAAT	G. G C G	TTGTC	A C.C A T T	TTAC	TGTAT	TTGTC	A 1 A A A A A T · A A A A	AAATTC	cohl_ai2.seq
						•	-			
	CTCCAAT	TAAA	TAAATI	L C V V V C	AAGCT	CCAAA	GGTAA	GCGTAG	GTACGC	Majority
·	<u> </u>	2160		2170		2180		2190	2200)
2151	CTCCAAT	TTAAA	TAAATT	T G A A.A G	AAGC-7	CCAAA	GGTAA	GCGTAG	GTACEC	coht at2 sea
2151	CTCCAAT	TTAAA	LTAAÁTT	T G A A A G	AAGCT	CCAAA	GGTAA	GCGTAG	GTACGC	a909_ai2.seq
						-			•	_
	GAAAAAA		101011		AICCA		TACTG	C G G T T	GTGGAA	Kajority
		2210	<u> </u>	2220	· · ·	2230		2240	2250	
2201 2201	GAAAAAA	ACCTI	TGTCTT	гстссс	ATCCA	GACT.T	TACTG	TCGGTT	G T G G A A	cohl_ai2.seq
4201	GAAAAAA	A C C I I	. reicri	i C I C·Ç c	ATCCA	GACTT	TACT.G	rec _. c r r	GTGGAA	a909_a12.seq
	TCTCACC	CATO	AGCTTT	CCCTC	GCGGA	CTGAT	GCTTC	CAACT	GACAAA	Majority
•		2260		2270		2280		2290	2300	
2251	TCTCACC	LCATO	AGETTI		CCCCA		C C T T C			
2251	TCTCACC	CATO	AGCTTI	CCCTC	GCGGA	CTGAT	GCTTC	ACAACI	GACAAA	cohl_al2.seq
			•		•				•	
	TAAGTTG	AAGE	GATTAC	cecce	GTCGG	CAATT	A C A C C C	TGCCC	TGAAGA	Kajority'
		2310		2320		2330		2340	2350	
2301	TAAGTTG	AAGC	GATTAC	CGCCG	GTCGG	GAATT	ACACC	TGCCC	T G A A G.A	cohl_al2.seq
5301	TAAGTTĠ	AAGC	GATTAC	ccccc	GTCGG	GAATT.	AEACC	CTGCCC	TGAAGA:	a909_a12.seq
	CACCTATA	GCAT	AACAAA		CTTGC	AATTC	CAACTI		A T C A C T :	V-1
	•	2360		2370	•	• •				
2351	CACCTAT		. 4 4 0 4 4 4	•		2380		2390	2400	
2351	CACCTATA	GCAT			CTTGC	AATTG	CAAGET	TTTTA	ATCACT	cohl_a12.seq
								•		
	AATTAGTA	GTAG	ATTGTA	TAATA	TTAAT	TTTTA	ACATCA	ATTAA	TTGACA	Majority
		2410		2420		.2430		2440	2450	,
2401	AATTAGTA	GTAG	ATTGTA	TAATA	TTAAT					nátil al2 ása
2401	· A A T T A G T A	GTAG	ATTGTA	TAATA	TTAAT	TTTTA	ACATCA	LATTAA	T T G A C A a	a909 ai2 sec
		:							•	
	GCGGACTA		TUTAGE	TACTC	CTCCC	TTTGT	A C' A A G I	VVVCV	AGCTTAI	lajority
•		. 2460		2470		2480		2490	2500	
2451	GCGCACTA	ATAC	TCTAGC	TACTC	CTGCC	TTTGT	A C A A G 7	AAACA	AGCTTA	coht <u>.</u> ä12.seg
.2451	G.C.G.C.A.C.T.A	ATAC	T C T A G.C	TACTC	CTCCC	TTTGT	ACAAGI	AAACA	A G C T T A 7	a909_ai2.seq
. •	AGTCCCAA	TGAT	тетете	ATGTG	ė c a c t					
٠.		2510						•		
				2520	-	2530		2540	2550	
2501 · 2501	AGTCCCAA	TCAT	TGTCTG	ATGTG	GCAGT	TTTAT	AAACTI	TTTCA	ATCGCT	cohi_ai2.seq
2001	AGTCCCAA		161616	KIGIG	CCAGT.	TTATA	RAACTI	TTTCA	ATCGCT	a909_a12.seq
	GTTCGTTC	AATA	ATTTCT	CTATT	ACTGA	TTTTGT	r a g t g a	TAGAT	TTGCCC	lalority .
		2560		2570		2580		2590		
.2551	GTTGGTTG		<u> </u>	. 1	1070			-	2600	
2551	GTTGGTTC GTTGGTTC	ATA	ATTTCT	CTATT	ACTGA	111167 TTTTC7	LAGTGA LAGTC4	TAGAT	TTGCCCC	conf_al2.seq
	_	•	-							www.are.sed

		2000/070010				1 6 17 6 8 2 0
	IGIIGALA.	Godin'T G iT Mark.	A-A F-A A-A-O XIT'Y	CGTTCCCATA	LTCTACATTTTT	TAAAG Wajority
		2610	2620	2630	2640	2650
2601	TGTTGTA	GTTGTAA	AATAAACAT	CCGTTCCCATA	ATCTACATITT	
2601	TGTTGTA	GTTGTAA	AATAAACAT(CCGTTCCCATA	ATCTACATTTTT	TAAAG cohl_a12.seq TAAAG a909_a12.seq
-						
		2660			CACCATGTTAT	TAGTT Majority
2001	0.1		2670	2680	2690	2700
2651 2651	CATCAAA	ATGATAA	G G A A A A T T A 1	GCGCACAAA	CACCATGTTAT	TAGTT cohi_ai2.seq
		A LOXIAN	GGAAAAIIAI	GCGCACAAA1	CACCATGTTAT	TAGTT a909_a12.seq
	AAATAAG	AACCATA	A T A C C T T G T A	GGCGTTTTAG	ACAGTTGTTCA	A A A C T Valority
	•	2710	2720	2730	2740	•
2701	AAATAAG	AACCATA	ATACCTTCTA			A A A C T cohl_ai2.seq
2701	AAATAAG	AACCATA	ATACCTTGTA	GGCGTTTTAG	GACAGTT GTT CA	A A A C T coh1_a12.seq A A A C T a909_a12.seq
	AIAAIIX	GUAGUTA	CCGCTAAATG	CAGTTTTAAG	TTCGGAATATC	C A G A G Majority
		2760	2770	2780	2790	2800
2751	ATAATTA	GCAGCTAC	CCGGTAAATG	CAGTTTTAAG	TTCGGAATATC	CAGAG cobl at 2 sea
2751	VIVVIIV	GCAGCTAC	CCGGTAAATG	CAGTTTTAAG	TTCGGAATATC	CAGAG a909_a12.seq
					AGGTAATTCTC	
		2810	2820	2830	•	•
2801	TTCCCAA				2840	2850
2801	TTCCCAA	GTAATCT	STTTTATCCA	ACTTTTTAC	A G G T A A T T C T C A G G T A A T T C T C	CATTT cohi_ai2.seq
	TOTORACE		TGATGCGTA	ATAGATTAT	CAACCGCCTTG	A C A A T Najority
		2860	2870	2880	2890	2900
2851 2851	TCTGAAC	CCTTTACT	TGATGCGTA	ATAGATTAT	CAAGCACCTTG	A C A A T cohi_ai2.seq
			TONIOCGIA	A I A G A I I T. A T	CAAGEGEETTG	ACAAT a909_a12.seq
	ATCCTCAC					
•	KIGCIGAC	AAGIIAA	ATCAGCTTG	ATGCGCCTGA	TTAATATTATA.	CCAAC Majority
	RIGUIGA	2910	2920	ATGCGCCTGA 2930		
	ATGCTGAC	2910 GAAGTTAA	2920 A T C A G C T T G	2930 .	2940	2950
	ATGCTGAC	2910 GAAGTTAA	2920 A T C A G C T T G	2930 .	2940	2950
	ATGCTGAC	2910 GAAGTTAA GAAGTTAA	ATCAGCTTG ATCAGCTTG	2930 A T G C G C C T G A A T G C G C C T G A	2940 TTAATATTATA (TTAATAT TATA (2950 CCAAC coht_ai2.seq CCAAC a909_ai2.seq
	ATGCTGAC	2910 G A A G T T A A G A A G T T A A G A T T C C A G	2920 A T C A G C T T G A T C A G C T T G A A C T T A C C A	2930 A T G C G C C T G A A T G C G C C T G A G A A T G A T T C C	2940 T T A A T A T T A T A A T T A A T A T T A T A	2950 C C A A C cohi_ai2.seq C C A A C a909_ai2.seq A A A A A Majority
2901 2901	ATGCTGAC	2910 G A A G T T A A G A A G T T A A G A T T C C A G 2960	2920 A T C A G C T T G A T C A G C T T G A A C T T A C C A 2970	2930 A T G C G C C T G A A T G C G C C T G A G A A T G A T T C C 2980	2940 T T A A T A T T A T A A T T A A T A T T A T A	2950 C C A A C cohl_ai2.seq C C A A C a909_ai2.seq A A A A A Majority 3000
2901 2901 2951	ATGCTGACATAG	2910 G A A G T T A A G A A G T T A A G A T T C C A G 2960 G A T T C C A G	2920 A T C A G C T T G A T C A G C T T G A A C T T A C C A 2970 A A C T T A C C A	2930 A T G C G C C T G A A T G C G C C T G A G A A T G A T T C C 2980	2940 T T A A T A T T A T A A T T A A T A T	2950 C C A A C coht_a12.seq C C A A C a909_a12.seq A A A A A Majority
2901 2901 2951	CCCAATAG	2910 G A A G T T A A G A A G T T A A G A T T C C A G 2960 G A T T C C A G A T T C C A G	2920 A T C A G C T T G A T C A G C T T G A A C T T A C C A 2970 A A C T T A C C A A A C T T A C C A	2930 A T G C G C C T G A A T G C G C C T G A G A A T G A T T C C 2980 G A A T A A T T C C G A A T G A T T C C	2940 TTAATATTATA TTAATATTATA TTAATATTATA CAGTATCGCTAA 2990 GAGTATAGCTAA NAGTATCGCTAA	2950 C C A A C cohl_a12.seq C C A A C a909_a12.seq A A A A A Majority 3000 A A A A A cohl_a12.seq A A A A A a909_a12.seq
2901 2901 2951	CCCAATAG	2910 G A A G T T A A G A A G T T A A G A T T C C A G 2960 G A T T C C A G A T T C C A G	2920 A T C A G C T T G A T C A G C T T G A A C T T A C C A 2970 A A C T T A C C A A C T T A C C A	2930 A T G C G C C T G A A T G C G C C T G A G A A T G A T T C C 2980 G A A T A A T T C C G A A T G A T T C C	2940 T T A A T A T T A T A A T T A A T A T	2950 C C A A C cohl_a12.seq C C A A C a909_a12.seq A A A A A Majority 3000 A A A A A cohl_a12.seq A A A A A a909_a12.seq
2901 2901 2951 2951	CCCAATAG	2910 GAAGTTAA GAAGTTAA GATTCCAG 2960 GATTCCAG ATTCCAG ATATCTT 3010	2920 A T C A G C T T G A T C A G C T T G A A C T T A C C A 2970 A A C T T A C C A A C T T A C C A C T A A T C A C G 3020	2930 A T G C G C C T G A A T G C G C C T G A G A A T G A T T C C 2980 G A A T A A T T C C T C T T C T T C T C C 3030	2940 T T A A T A T T A T A A A T A A T A T	2950 C C A A C cohi_ai2.seq C C A A C a909_ai2.seq A A A A A Majority 3000 A A A A A cohi_ai2.seq A A A A A a909_ai2.seq A T T A Majority 3050
2901 2901 2951 2951 3001	ATGCTGAC ATACTGAC CCCAATAC CCCAATAC TTTGCTGA	2910 A A G T T A A A A G T T A A A T T C C A G 2960 A T T C C A G A T A T C T T 3010	2920 A T C A G C T T G A T C A G C T T G A A C T T A C C A 2970 A A C T T A C C A A A C T T A C C A C T A A T C A C G 3020 C T A A T C A C G	2930 A T G C G C C T G A A T G C G C C T G A G A A T G A T T C C 2980 G A A T A A T T C C T C T T C T C C 3030 T C T T C T T C T C T C	2940 TTAATATTATA TTAATATTATA TTAATATTATA CAGTATCGCTAA 2990 GAGTATAGCTAA AAGTATCGCTAA CATTTTAAAGGCT 3040	2950 C C A A C cohl_ai2.seq C C A A C a909_ai2.seq A A A A Majority 3000 A A A A A cohl_ai2.seq A A A A A a909_ai2.seq A T T A Majority 3050
2901 2901 2951 2951	ATGCTGAC ATACTGAC CCCAATAC CCCAATAC TTTGCTGA	2910 A A G T T A A A A G T T A A A T T C C A G 2960 A T T C C A G A T A T C T T 3010	2920 A T C A G C T T G A T C A G C T T G A A C T T A C C A 2970 A A C T T A C C A A A C T T A C C A C T A A T C A C G 3020 C T A A T C A C G	2930 A T G C G C C T G A A T G C G C C T G A G A A T G A T T C C 2980 G A A T A A T T C C T C T T C T C C 3030 T C T T C T T C T C T C	2940 TTAATATTATAA TTAATATTATAA TAATATTATAA GAGTATCGCTAA 2990 GAGTATAGCTAA AAGTATCGCTAA	2950 C C A A C cohl_ai2.seq C C A A C a909_ai2.seq A A A A Majority 3000 A A A A A cohl_ai2.seq A A A A A a909_ai2.seq A T T A Majority 3050
2901 2901 2951 2951 3001	ATGCTGAC ATACTGAC CCCAATAG CCCAATAG CCCAATAG TTTGCTGA TTTGCTGA	2910 GAAGTTAA GAAGTTAA GATTCCAG 2960 GATTCCAG GATTCCAG GATTCCAG ATATCTT 3010 ATATCTT	2920 A T C A G C T T G A T C A G C T T G A A C T T A C C A 2970 A A C T T A C C A A A C T T A C C A C T A A T C A C G 3020 C T A A T C A C G C T A A T C A C G	2930 A T G C G C C T G A A T G C G C C T G A G A A T G A T T C C 2980 G A A T A A T T C C G A A T G A T T C C T C T T C T T C T C T C T T C T T C T C	2940 T T A A T A T T A T A A A T A A T A T	2950 C C A A C cohi_ai2.seq C C A A C a909_ai2.seq A A A A A Majority 3000 A A A A A cohi_ai2.seq A A A A A a909_ai2.seq A T T A Majority 3050 A T T A cohi_ai2.seq A T T A a909_ai2.seq A T T A a909_ai2.seq
2901 2901 2951 2951 3001	ATGCTGAC ATACTGAC CCCAATAG CCCAATAG CCCAATAG TTTGCTGA TTTGCTGA	2910 GAAGTTAA GAAGTTAA GATTCCAG 2960 GATTCCAG GATTCCAG GATTCCAG ATATCTT 3010 ATATCTT	2920 A T C A G C T T G A T C A G C T T G A A C T T A C C A 2970 A A C T T A C C A A A C T T A C C A C T A A T C A C G 3020 C T A A T C A C G C T A A T C A C G	2930 A T G C G C C T G A A T G C G C C T G A G A A T G A T T C C 2980 G A A T A A T T C C T C T T C T T C T C C T C T T C T T C T C	2940 T T A A T A T T A T A A A A T A T A T	2950 C C A A C cohl_a12.seq C C A A C a909_a12.seq C A A A A Majority 3000 A A A A A cohl_a12.seq A A A A A a909_a12.seq A T T A Majority 3050 A T T A cohl_a12.seq A T T A a909_a12.seq A T T A a909_a12.seq T A C T Majority
2901 2901 2951 2951 3001 3001	ATGCTGAC ATMCTGAC CCCAATAG CCCAATAG CCCAATAG TTTGCTGA TTTGCTGA TTTAAACAC	2910 A A G T T A A A A G T T A A A T T C C A G 2960 A T T C C A G A T T C C T T 3010 A T A T C T T A G A A G T C 3060 A C A A G T C	2920 A T C A G C T T G A T C A G C T T G A T C A G C T T G A A C T T A C C A 2970 A A C T T A C C A A C T T A C C A C T A A T C A C G C T A A T C A C G C T A A T C A C G C T G A C A T A A 3070	2930 A T G C G C C T G A A T G C G C C T G A G A A T G A T T C C 2980 G A A T A A T T C C T C T C T T C T C T C T C T C	2940 T T A A T A T T A T A A A T A A T A T	2950 C C A A C cohl_a12.seq C C A A C a909_a1Z.seq C A A A A Majority 3000 A A A A A cohl_a12.seq A A A A A a909_a1Z.seq A T T A Majority 3050 A T T A cohl_a12.seq A T T A a909_a1Z.seq T A T T A wayority 3050 A T T A cohl_a12.seq T A T T A wayority A T T A ayority 3100
2901 2901 2951 2951 3001 3001	ATGCTGAC ATMCTGAC CCCAATAG CCCAATAG CCCAATAG TTTGCTGA TTTGCTGA TTTAAACAC	2910 A A G T T A A A A G T T A A A T T C C A G 2960 A T T C C A G A T T C C T T 3010 A T A T C T T A G A A G T C 3060 A C A A G T C	2920 A T C A G C T T G A T C A G C T T G A T C A G C T T G A A C T T A C C A 2970 A A C T T A C C A A C T T A C C A C T A A T C A C G C T A A T C A C G C T A A T C A C G C T G A C A T A A 3070	2930 A T G C G C C T G A A T G C G C C T G A G A A T G A T T C C 2980 G A A T A A T T C C T C T C T T C T C T C T C T C	2940 T T A A T A T T A T A A A T A A T A T	2950 C C A A C cohl_a12.seq C C A A C a909_a12.seq C C A A A A Majority 3000 A A A A A cohl_a12.seq A A A A A a909_a12.seq A T T A Majority 3050 A T T A cohl_a12.seq A T T A a909_a12.seq T A C T Majority 3100 T A C T cohl_a12.seq
2901 2901 2951 2951 3001 3001 3051	ATGCTGAC CCCAATAG CCCAATAG CCCAATAG TTTGCTGA TTTGCTGA TTTGCTGA TTTAAACAC TTAAAACAC	2910 A A G T T A A A A G T T A A A T T C C A G 2960 A T T C C A G A T A T C T T 3010 A T A T C T T A G A A G T C 3060 A G A A G T C A G A A G T C A G A A G T C	2920 A T C A G C T T G A T C A G C T T G A C A T A C C A 2970 A A C T T A C C A A A C T T A C C A C T A A T C A C G 3020 C T A A T C A C G C T A A T C A C G C T A A T C A C G C T G A C A T A A 3070 C T G A C A T A A C T G A C A T A A	2930 A T G C G C C T G A A T G C G C C T G A A T G C G C C T G A G A A T G A T T C C 2980 G A A T A A T T C C G A A T G A T T C C T C T T C T T C T C T C T T C T C	2940 T T A A T A T T A T A A T T A A T A T	2950 C C A A C cohi_ai2.seq C C A A C a909_ai2.seq A A A A Majority 3000 A A A A A cohi_ai2.seq A A A A A a909_ai2.seq A T T A Majority 3050 A T T A cohi_ai2.seq A T T A a909_ai2.seq T A C T kajority 3100 T A C T cohi_ai2.seq T A C T cohi_ai2.seq
2901 2901 2951 2951 3001 3001 3051	ATGCTGAC CCCAATAG CCCAATAG CCCAATAG TTTGCTGA TTTGCTGA TTTGCTGA TTTAAACAC TTAAAACAC	2910 A A G T T A A A A G T T A A 2960 A T T C C A G A T T C C A G A T T C T T 3010 A T A T C T T A G A A G T C 3060 A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C	2920 A T C A G C T T G A T C A G C T T G A T C A G C T T G A A C T T A C C A 2970 A A C T T A C C A A C T T A C C A C T A A T C A C G C T A A T C A C G C T A A T C A C G C T A A T C A C G C T A A T C A C G C T A A T C A C G C T A A T C A C G C T A A T C A C G C T A A T C A C G C T A A T C A C G C T A A T C A C G C T A C A T A A C T C A C A T A A A G C T T T C C C C	2930 A T G C G C C T G A A T G C G C C T G A A T G C G C C T G A G A A T G A T T C C 2980 G A A T A A T T C C G A A T G A T T C C T C T T C T T C T C T C T T C T C	2940 T T A A T A T T A T A A A T A A T A T	2950 C C A A C cohi_ai2.seq C C A A C a909_ai2.seq A A A A Majority 3000 A A A A A cohi_ai2.seq A A A A A a909_ai2.seq A T T A Majority 3050 A T T A cohi_ai2.seq A T T A a909_ai2.seq T A C T kajority 3100 T A C T cohi_ai2.seq T A C T cohi_ai2.seq
2901 2901 2951 2951 3001 3001 3051 3051	ATGCTGAC ATMCTGAC CCCAATAG CCCAATAG CCCAATAG TTTGCTGA TTTGCTGA TTTGCTGA TTTAAACAC TTAAAACAC TTAAAACAC	2910 A A G T T A A A A G T T A A A T T C C A G 2960 A T T C C A G A T T C C A G A T A T C T T 3010 A T A T C T T A G A A G T C	2920 A T C A G C T T G A T C A G C T T G A T C A G C T T G A A C T T A C C A A A C T T A C C A A A C T T A C C A C T A A T C A C G C T A A T C A C G C T A A T C A C G C T A A T C A C G C T A A T C A C G C T G A C A T A A A G C T T T C C C C 3120	2930 A T G C G C C T G A A T G C G C C T G A A T G A T T C C 2980 G A A T A A T T C C G A T T C C G A T T C C C T C T C T C C C T C T C T C	2940 T T A A T A T T A T A A A T A A T A T	2950 C C A A C cohl_a12.seq C C A A C a909_a12.seq C C A A C a909_a12.seq A A A A A Majority 3000 A A A A A cohl_a12.seq A A A A A a909_a12.seq A T T A Majority 3050 A T T A cohl_a12.seq A T T A a909_a12.seq T A C T Majority 3100 T A C T cohl_a12.seq T A C T a909_a12.seq T A C T a909_a12.seq C A C T Majority 3150
2901 2901 2951 2951 3001 3001 3051 3051	ATGCTGAC CCCAATAC CCCAATAC CCCAATAC CCCAATAC TTTGCTGA TTTGCTGA TTTAAACAC TTAAACAC TTAAACAC TTAAACAC TTAAACAC	2910 A A G T T A A A A G T T A A A T T C C A G 2960 A T T C C A G A T A T C T T 3010 A T A T C T T A G A A G T C 3060 A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C A A A C G G G A A A C G G G	2920 A T C A G C T T G A T C A G C T T G A C A T A C C A 2970 A A C T T A C C A A A C T T A C C A C T A A T C A C G C T A A T C A C G C T A A T C A C G C T A A T C A C G C T G A C A T A A 3070 C T G A C A T A A C T C A C A T A A C T C A C A T A A C T C A C A T A A C T C A C A T A A C T C A C A T A A C T C A C A T A A C T C A C C T T T C C C 3120 A G C T T T C C C C T C A C C T T T C C C C T C A C C T T T C C C C T C C C T T T C C C C	2930 A T G C G C C T G A A T G C G C C T G A A T G C G C C T G A G A A T G A T T C C 2980 G A A T A A T T C C G A A T G A T T C C T C T T C T T C T C T C T T C T C	2940 T T A A T A T T A T A A A T A A T A T	2950 C C A A C cohi_ai2.seq C C A A C a909_ai2.seq A A A A Majority 3000 A A A A A cohi_ai2.seq A A A A A a909_ai2.seq A T T A Majority 3050 A T T A cohi_ai2.seq A T T A a909_ai2.seq T A C T Kajority 3100 T A C T cohi_ai2.seq T A C T a909_ai2.seq T A C T a909_ai2.seq T A C T a909_ai2.seq T A C T Wajority 3150
2901 2901 2951 2951 3001 3001 3051 3051	ATGCTGAC CCCAATAC CCCAATAC CCCAATAC CCCAATAC TTTGCTGA TTTGCTGA TTTAAACAC TTAAACAC TTAAACAC TTAAACAC TTAAACAC	2910 A A G T T A A A A G T T A A A T T C C A G 2960 A T T C C A G A T A T C T T 3010 A T A T C T T A G A A G T C 3060 A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C A A A C G G G A A A C G G G	2920 A T C A G C T T G A T C A G C T T G A C A T A C C A 2970 A A C T T A C C A A A C T T A C C A C T A A T C A C G C T A A T C A C G C T A A T C A C G C T A A T C A C G C T G A C A T A A 3070 C T G A C A T A A C T C A C A T A A C T C A C A T A A C T C A C A T A A C T C A C A T A A C T C A C A T A A C T C A C A T A A C T C A C A T A A C T C A C A T A A C T C A C A T A A C T C A C C T T T C C C 3120	2930 A T G C G C C T G A A T G C G C C T G A A T G C G C C T G A G A A T G A T T C C 2980 G A A T A A T T C C G A A T G A T T C C T C T T C T T C T C T C T T C T C	2940 T T A A T A T T A T A A A T A A T A T	2950 C C A A C cohi_ai2.seq C C A A C a909_ai2.seq A A A A Majority 3000 A A A A A cohi_ai2.seq A A A A A a909_ai2.seq A T T A Majority 3050 A T T A cohi_ai2.seq A T T A a909_ai2.seq T A C T Kajority 3100 T A C T cohi_ai2.seq T A C T a909_ai2.seq T A C T a909_ai2.seq T A C T a909_ai2.seq T A C T Wajority 3150
2901 2901 2951 2951 3001 3001 3051 3101 3101	ATGCTGAC ATMCTGAC CCCAATAG CCCAATAG CCCAATAG CCCAATAG TTTGCTGA TTTGCTGA TTTAAACAC TTAAAACAC TTAAAACAC TTAAAACAC TGTCCAGT	2910 A A G T T A A A A G T T A A 2960 A T T C C A G A T T C C A G A T A T C T T 3010 A T A T C T T A G A A G T C 3060 A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C	2920 A T C A G C T T G A T C A G C T T G A T C A G C T T G A A C T T A C C A 2970 A A C T T A C C A A A C T T A C C A C T A A T C A C G 3020 C T A A T C A C G C T A A T C A C G C T A A T C A C G C T G A C A T A A C T G A C A T A A C T G A C A T A A A G C T T T C C C A G C T T T C C C A G C T T T C C C	2930 A T G C G C C T G A A T G C G C C T G A A T G C G C C T G A G C C T G A A T G C G A T G C G A T G C G A T G C G A T G C T C T C T C T C T C T C T C T C T	2940 T T A A T A T T A T A A A T A T A T A	2950 C C A A C cohi_ai2.seq C C A A C a909_ai2.seq C C A A C a909_ai2.seq C C A A A A Majority 3000 A A A A A cohi_ai2.seq A A A A A a909_ai2.seq A T T A Majority 3050 A T T A cohi_ai2.seq A T T A a909_ai2.seq T A C T Majority 3100 T A C T cohi_ai2.seq T A C T a909_ai2.seq C A C T Majority 3150 C A C T cohi_ai2.seq C A C T cohi_ai2.seq C A C T a909_ai2.seq
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2901 2901 2951 2951 3001 3001 3051 3101 3101	ATGCTGAC CCCAATAG CCCAATAG CCCAATAG CCCAATAG TTTGCTGA TTTGCTGA TTTAAACAC TTAAAACAC TTAAAACAC TTAAAACAC TGTCCAGT AATTGTCT	2910 A A G T T A A A A G T T A A 2960 A T T C C A G A T T C C A G A T A T C T T 3010 A T A T C T T A G A A G T C 3060 A G A A G T C A G A A G T C A G A A G T C A G A A G T C 3110 A A A C G G G C T T C T T T 3160 C T T C T T T	2920 A T C A G C T T G A T C A G C T T G A A C T T A C C A 2970 A A C T T A C C A A A C T T A C C A C T A A T C A C G 3020 C T A A T C A C G C T A A T C A C G C T A A T C A C G C T G A C A T A A C T G A C A T A A C T G A C A T A A C T G A C A T A C 3120 A G C T T T C C C T T T A G G T T T A 3170 T T T A G C T T T T	2930 ATGCGCCTGA ATGCGCCTGA ATGCGCCTGA GAATGATTCC 2980 GAATAATTCC TCTTCTTCTC 3030 TCTTCTTCTC TCTTCTTCTC TTAGTATAGG TTAGTATAGG TTTGTCTGAT 3130 TTTGTCTGAT GCATTTAAAA	2940 T T A A T A T T A T A A A T A A T A T	2950 C C A A C cohi_ai2.seq C C A A C a909_ai2.seq C C A A C a909_ai2.seq C C A A C a909_ai2.seq A A A A A Majority 3000 A A A A A cohi_ai2.seq A A T A Majority 3050 A T T A cohi_ai2.seq A T T A a909_ai2.seq T A C T kajority 3100 T A C T cohi_ai2.seq T A C T a909_ai2.seq C A C T Majority 3150 C A C T cohi_ai2.seq C A C T a909_ai2.seq T C A C T a909_ai2.seq T C A C T a909_ai2.seq T C A C T a909_ai2.seq
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2901 2901 2951 2951 3001 3001 3051 3101 3101 3151 3151	ATGCTGAC CCCAATAC CCCAATAC CCCAATAC CCCAATAC TTTGCTGA TTTGCTGA TTTAAACAC TTAAACAC TTAAACAC TTAAACAC TTGTCCAGT TGTCCAGT TGTCCAGT	2910 A A G T T A A A A G T T A A A T T C C A G 2960 A T T C C A G A T A T C T T 3010 A T A T C T T A G A A G T C 3060 A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C A G A A G T C C T T C T T T 3160 C T T C T T T C T T C T T T	2920 A T C A G C T T G A T C A G C T T G A A C T T A C C A 2970 A A C T T A C C A A A C T T A C C A C T A A T C A C G C T A A T C A C G C T A A T C A C G C T A A T C A C G C T G A C A T A A C T C A C A T A A C T C A C A T A A C T C A C A T A C 3120 A G C T T T C C C T T T A G C T T T A T T T A G C T T T A	2930 ATGCGCCTGA ATGCGCCTGA ATGCGCCTGA GAATGATTCC 2980 GAATAATTCC GAATGATTCC TCTTCTTCTC 3030 TCTTCTTCTC TCTTCTTCTC TAGTATAGG TTAGTATAGG TTAGTATAGG TTAGTATAGG TTTGTCTGATG 3130 TTTGTCTGATG GCATTTAAAA	2940 T T A A T A T T A T A A A T A A T A T	2950 C C A A C cohi_ai2.seq C C A A C a909_ai2.seq C C A A C a909_ai2.seq A A A A A Majority 3000 A A A A A cohi_ai2.seq A A T A Majority 3050 A T T A Cohi_ai2.seq A T T A a909_ai2.seq T A C T Cohi_ai2.seq T A C T a909_ai2.seq T C A A Majority 3200 T C A A cohi_ai2.seq
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		CCCTT	GAGGA	AGATTG		ACAATA		AGCCG	G T A · A A T T	ATCAA Hajori	ty
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		TATTT				GTTTA		G T T.A G A	TCATCG	TCTTT Majori	ty
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Thurs	day, July 29, 2004 6:49 PM				
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	3910	3920	3930	3940	3950
3901	TATTAACCCCA	TATCCTCTACA	_		
3901	TATTAACACCA	TATEGTETACA	C G T C A C C A A A G T C G T C A C C A A A G T	TTGGTAGTCTTT	ACCT coh1_a12.seq
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3051	TTAACAATTTC				4000
3951	TTAACAATTTC		A A T C A T C C G G T T T	TAACTGTTCTGA	TTTC cohi_ai2.seq
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	CTCCACCTTTT	AACITATCCAA	ATCAGAAAAAG	CTTGAAGAGGG	TAAA cohi_ai2.seq
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	CCTCTATGTCC	TGATAAAATAG	AATGAGTTGAGT	TCCTCCAATTC	AAG Valoetty
	. 4110	4120	4130	•	
1101	<u> </u>			4140	4150
4101	CCTCTATGTCC	TGATAAAATAG	AATGAGTTGAGT	TCCTCCAATTG	GAAG cohl_ai2.seq
1101	, borner a rolle c	IGNIKAKAIAG	A A T G A G.T T G A G T (T C C T C C A A T T G (GAAC a909_ai2.seq
. •	ACTACTTCCTT	CTAAATGACCA	ATAGAAGTTTGAA	G C'A-C T'T T T T C A C	TTC Volceton
	4160	4170	· ·		
4		-	4180	4190	4200
4151	ACTACTTCCTT	CTAAATGACCA	ATAGAAGTTTGAA	GCACTTTTTCAC	TTG cohl_ai2.seq
,	NOT NOT TOUT I	CIRARIGACCA	ATAGAAGTTTGAA	GCACLETTTTCAC	CTTG a909_a12.seq
-	TACCATGATAA	AGTGGTAATTT	TATGTT TATCTT	GGAATTGAAATA	T A A Majority
	4210	. 4220	.4230	4240	
4201	TACCATCATAA				4250
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	4260	. 4270 .	4280.	4290	4300
4251	CCCATATTACC	CGTTTTATCGA	TAGCCAGTTGTGA		
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	CTCTTGGTTAG	TCATGTGCCAC	TTCATTCCTGAAG	TTTTAAATTGCT	TAT Majority
	4310	4320	4330	4340	4350
4301	CTCTTGGGTAG	TCATCTCCCAC	TCATTCCTGAAG		
4301	CTCTTGGTCAG	TCATGTGCCAC	TTCATTCCTGAAG	TTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTT	IAI CONL_aiz.seq
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4401	4360 TATATTETTTE TATATTETTTE TATATTETTTE 4410 TGCGTTACGCG TGCGTTACGCG ATTCCAATAAT: 4460	G C T C G G T T A A T A 4370 G C T C G G T T A A T A G C T C G G T T A A T A C T C T T G G T A A T A G T C T T G G T A A T C G T C T T G G T A A T C G T C T T G G T A A T C G T C T T G G T A A T C G T C T T G G T A A T C G T C T T G G T A A T C G T C T T G G T A A T C 4470	4380 A TTTTTTTATAG A ATTTTTTTTATAG A ATTTTTTTTATAG A ATTTTTTTTATAG C ATAATCGCTCG 4430 C C ATAATCGCTCG C C ATAATCGCTCG	T C G T T T T C A T C C 4390 T C G T T T T C A T C C T C G T T T T C A T C C A G A T T G G T G A A A 4440 A G A T T G G T G A A A A G A T T G G T G A A A A G A T T G G T G A A A A G A T T G G T C A A A A G A T T G G T C A A A A G C C T A C C C C C A	A T A Majority 4400 A T A cohl_ai2.seq A T A a909_ai2.seq T G A Majority 4450 T G A cohl_ai2.seq T G A deltai2.seq
4401	4360 TATATTETTTE TATATTETTTE TATATTETTTE 4410 TGCGTTACGCG TGCGTTACGCG ATTCCAATAAT 4460 ATTCCAATAAT	G C T C G G T T A A T A 4370 G C T C G G T T A A T A G C T C G G T T A A T A G T C T T G G T A A T A G T C T T G G T A A T A G T C T T G G T A A T A G T C T T G G T A A T A G T C T T G G T A A T A G T C T T G G T A A T A G T C T T G G T A A T A G T C T T G G T A A T A G T A G C A A G T G A A A T A G C A A G T G A A A	4380 A T T T T T T T T A T A G A A T T T T T T T T A T A G C A T A A T C G C T C G 4430 C C A T A A T C G C T C G C C A T A A T C G C T C G C C A T A A T C G C T C G G A T A A G C C A T T A 4480.	T C G T T T T C A T C C 4390 T C G T T T T C A T C C T C G T T T T C A T C C A G A T T G G T G A A A 4440 A G A T T G G T G A A A A G A T T G G T G A A A A G A T T G G T C A A A A G C C T A C C C C C A	A T A Majority 4400 A T A coh1_a12.seq A T A a909_a12.seq T G A Majority 4450 T G A coh1_a12.seq C T G Majority 4500 C T G coh1_a12.seq
4401 4401 4451	4360 TATATTETTTG TATATTETTTG TATATTETTTG 4410 TGCGTTACGCG TGCGTTACGCG ATTCCAATAATT ATTCCAATAATT ATTCCAATAATT	G C T C G G T T A A T A 4370 G C T C G G T T A A T A G C T C G G T T A A T A 4420 G T C T T G G T A A T C G T C T T G G T A A T C G T C T T G G T A A T C G T C T T G G T A A T C G T C T T G G T A A T C G T C T T G G T A A T C G T C T T G G T A A T C G T C T T G G T A A T C A G C A A G T G A A C T A G C A A G T G A A C	4380 A T T T T T T T T A T A A A A T T T T	4390 T C G T T T T C A T C C T C G T T T T C A T C C T C G T T T T C A T C C A G A T T G G T G A A A 4440 A G A T T G G T G A A A A G A T T G G T G A A A A G A T T G G T G A A A A G C C T A C C C C C A A G C C T A C C C C C A A G C C T A C C C C C C	A T A Majority 4400 A T A coh1_a12_seq A T A a coh1_a12_seq A T A a a a a a a a a a a a a a a a a a
4401 4401 4451	4360 TATATTETTTG TATATTETTTG TATATTETTTG 4410 TGCGTTACGCG TGCGTTACGCG ATTCCAATAATT ATTCCAATAATT ATTCCAATAATT	G C T C G G T T A A T A 4370 G C T C G G T T A A T A G C T C G G T T A A T A 4420 G T C T T G G T A A T C G T C T T G G T A A T C G T C T T G G T A A T C G T C T T G G T A A T C G T C T T G G T A A T C G T C T T G G T A A T C G T C T T G G T A A T C G T C T T G G T A A T C A G C A A G T G A A C T A G C A A G T G A A C	4380 A T T T T T T T T A T A A A A T T T T	4390 T C G T T T T C A T C C T C G T T T T C A T C C T C G T T T T C A T C C A G A T T G G T G A A A 4440 A G A T T G G T G A A A A G A T T G G T G A A A A G A T T G G T G A A A A G C C T A C C C C C A A G C C T A C C C C C A A G C C T A C C C C C C	A T A Majority 4400 A T A coh1_a12_seq A T A a coh1_a12_seq A T A a a a a a a a a a a a a a a a a a
4401 4401 4451	4360 TATATTETTTG TATATTETTTG TATATTETTTG 4410 TGCGTTACGCG TGCGTTACGCG ATTCCAATAATT ATTCCAATAATT ATTCCAATAATT	G C T C G G T T A A T A 4370 G C T C G G T T A A T A G C T C G G T T A A T A 4420 G T C T T G G T A A T C G T C T T G G T A A T C G T C T T G G T A A T C G T C T T G G T A A T C G T C T T G G T A A T C G T C T T G G T A A T C G T C T T G G T A A T C G T C T T G G T A A T C A G C A A G T G A A C T A G C A A G T G A A C	4380 A T T T T T T T T A T A A A T T T T T T	4390 T C G T T T T C A T C C T C G T T T T C A T C C T C G T T T T C A T C C A G A T T G G T G A A A 4440 A G A T T G G T G A A A A G A T T G G T G A A A A G C C T A C C C C C A 4490 A G C C T A C C C C C A A G C C T A C C C C C A	A T A Majority 4400 A T A coh1_a12.seq A T A a909_a12.seq A T A a909_a12.seq T G A Majority 4450 T G A coh1_a12.seq T C A a909_a12.seq C T G Majority 4500 C T G coh1_a12.seq C T G a909_a12.seq T T C Majority
4401 4401 4451 4451	4360 TATATTETTTE TATATTETTTE TATATTETTTE 4410 TGCGTTACGCG TGCGTTACGCG ATTCCAATAATT ATTCCAATAATT ATTCCAATAATT ATTCCAATAATT ATTCCAATAATT ATTCCAATAATT	G C T C G G T T A A T A 4370 G C T C G G T T A A T A G C T C G G T T A A T A 4420 G T C T T G G T A A T C G T C T T G G T A A T C G T C T T G G T A A T C G T C T T G G T A A T C G T C T T G G T A A T C G T C T T G G T A A T C 4470 T A G C A A G T G A A C T A G C A A G T G A A C A C A A G C A A A A T C 4520	ATTTTTTATAG 4380 ATTTTTTTATAG ATTTTTTTATAG CCATAATCGCTCG 4430 CCATAATCGCTCG CCATAATCGCTCG CCATAATCGCTCG GATAACCCATTA 4480 GGATAAGCCATTA 6 GATAAGCCATTA	4390 T C G T T T T C A T C C T C G T T T T C A T C C A G A T T G G T G A A A 4440 A G A T T G G T G A A A A G A T T G G T G A A A A G A T T G G T G A C C A G C C T A C C C C C A A G C C T A C C C C C A T G T C T T A T T T T T 4540	A T A Majority 4400 A T A coh1_a12.seq A T A coh1_a12.seq A T A a909_a12.seq T G A Majority 4450 T G A coh1_a12.seq T G A a909_a12.seq C T G Majority 4500 C T G coh1_a12.seq C T G a909_a12.seq T T C Majority 4500 U T G coh1_a12.seq U T G Majority 4500 U T G Majority
4401 4401 4451	4360 TATATTETTTE TATATTETTTE TATATTETTTE TGCGTTACGCG 4410 TGCGTTACGCG ATTCCAATAATT ATTCCAATAATT ATTCCAATAATT ATTCCAATAATT CAATTATAGTGA CAATTATAGTGA CAATTATAGTGA	G C T C G G T T A A T A 4370 G C T C G G T T A A T A G C T C G G T T A A T A 4420 G T C T T G G T A A T A G T C T T G G T A A T A G T C T T G G T A A T A G T C T T G G T A A T A G T C T T G G T A A T A G T C T T G G T A A T A 4470 T A G C A A G T G A A A T A G C A A G T G A A A 4520 A C A A G C A A A A T C A C A A G C A A A A T C	4380 A T T T T T T T T A T A A A T T T T T T	T C G T T T T C A T C C 4390 T C G T T T T C A T C C T C G T T T T C A T C C A G A T T G G T G A A A 4440 A G A T T G G T G A A A A G A T T G G T G A A A A G A T T G G T G A A A A G C C T A C C C C C A G C C T A C C C C C A C G C C T A C C C C C C T G T C T T A T T T T T 4540 T G T C T T A T T T T T T	A T A Majority 4400 A T A cohi_ai2.seq A T A cohi_ai2.seq A T A a909_ai2.seq T G A Majority 4450 T G A cohi_ai2.seq T G A a909_ai2.seq C T G Majority 4500 C T G cohi_ai2.seq C T G a909_ai2.seq T T C Majority 4550 T T C Cohi_ai2.seq T T C Majority

Align Thur	ment Report of W	O <u>. 200</u> 6/0783	18 in method with Weighte	nd residue weight table.	87	PCT/US20
		TTTAAA		TTGETAGCCCAT	CTTATTAAGAA	CGTA Majority
4551	4 T 4 T 4 T	4560	4570	4580	4590	4600
4551	ATATAT	T T A A A T T T A A A T	CTGTACCACT	TTGCTAGCCCAT	CTTATTAAGAA	CGTA cohl_al2.seq CGTA a909_ai2.seq
	AACGAC	GACGAGC		ATACCTGCTCCT	ATTACTAAAAT	FGCA Majority
4601	AACGAC	GACGAGC	4620 A A C A A C C A C C	ATACCTGCTCCT	4640	4650
4601	AACGAC	GACGAGC	AACAAGCACG	ATACCTGCTCCT		ГССА coh1_al2.seq ГССА a909_al2.seq
	CCTATA	ATGTAGA	AAATTGTTGT.	A C C A A T A C C A C C T	C C T T G A A G G C A A	CTC Majority
4651	CCTATA	4660	4670	4680	4690	4700
4651	CCTATA	ATGTAGA		A C C A A T A C C A C C T A C C A A T A C C A C C T	T G T T G A A G G C A A T G T T G A A G G C A A	CTC cohl_al2.seq CTC a909_al2.seq
	AGTACC	T T G T.T A 4710		TTGGGTTAACTAA	AAGGTTATCTO	A A T Majority
4701	AGTACC	·	TTTCAACAG	4730	4740	4750
4701	A G T A C C	TTTGTTA	·	TTGGGTTAACTAA TTGGGTTAACTAA	AAGGTTATCTO	A A T a909_a12.seq
	TAGICG	4760	4770	CTAAAATAACCT	•	TCT Majority
4751			GGCTCCATCT	4780 C T A A A A T A A C C T	TCTGAGAGTTA	4800
4751	TAGTCGT	***	GGCTCCATCT	CTAAAATAACCT	TCTGAGAGTTA	TCT a909_a12.seq
	AACAAA1	TGTAACC		TTTTTCTCAACT	AGATAGTATGT	A.C.C. Majority
4801	AACAAA	4810	4820 CTAAGGGAGC	4830	4840	4850
4801	AACAAA	TTGTAAC	CTAAGGGAGCC	CTTTTTCTCAACT	AGATAGTATGT	A C C cohl_ai2.seq A C C a909_ai2.seq
	1101110	4860	•	TATACCATCTGC		A T T Najority
48 5 1	TTCTTTC	AAGCCTC	4870 T A A T G G T A A T	4880 ·	4890	4900
4851				TATACCATCTGC TATACCATCTGC	TECTGTTGTAT	A T T cohl_a12.seq A T T a909_a12.seq
•		4910	. 4920	ATTCAACGTTAT		A A G Majority
4901	CTGTTGC	ATTAGET	TCTGTGCCCC	ATTCAACGTTAT	4940. TTCTATCCTTA	4950
4901				ATICAACGITAT	TTGTATCGTTA	A A G a909_ai2.seq
		4960	· 4970	TTTAAAACAAAT 4980	•	•
4951 4951	TTTAGAA TTTAGAA	ATTGACC	CGTAGCATTC			T A A cohl_al2.seq
				TTTTTTATAGT		T A A a909_ai2.seq
	•	5010	5020	5030	5040 .	CCC Majority 5050
5001	TGAAGCT	TTTGTG.G	AACCATCAAT	TTTTTTTATACT	1 1 7 7 7 7 1 7 7 7 7 7 7 7 7 7 7 7 7 7	
5001			W. C. C. V. I. C. W. V. I.	TILL THE PATAGE.	A'A T T T'G A C C A'T	C C C a909_a12.seq
٠	TCACIGI	5060		CATCATTGCTAG		A T G Majority
5051	TCACTGT		TGACCTGGGT	CATCATTGCTAG	5090	5100
:			T U K C C I G G G I	CALCALIGGIAG	IATTGGGGTTG	A T G a909_a12.seq
•	GTCGCAA	TGTTTGT.	ATTTTCTGGT	AAATCAGCTGAA	CCTGGTTTAGC	FCC Majority
	CTCCCAA	5110 T.C.T.T.T.O.T.	5120	5130	5140	5150
				A A A T C A G C T G A A A	CCTGGTTTAGC:	ГСС a909_a12.seq
	ACTCTTT.	AATACTC		GACTGTGATTGT	TTTATTCCCT1	AT Majority
151	ACTCTTT	. 5160	5170 C T C T A T A A C T	5180 ·	5190	5200
5151	ACTCTTT	AATACTC	CTGTATAAGT	G A C T G T G A T T G T / G A C T G T G A T T G T /	A T T T A T T C C C T 1 A T T T A T T C C C T 1	FAT cohl_al2.seq FAT a909_al2.seq

Thun	sday, July 29, W. V. 4				·	FC1/US200
	AAAAAA.	TO A T C A	THE C'THE C'X	TTTTGAGTATT	TCCGGTTGGAGT	ATTC Hatester
	Har Bent	5210	5220	5230		• .
5201	444444		•		5240	5250
5201	AAAAAAA	SICAICA	I I A G C T C C A	TTTTGAGTATT	TCCGGTTGGAGT	ATTG cohi_ai2.seq
		····	IIAUCICCA	ITTIGAGIATT	TCCGGTTGGAGT	ATTG a909_a12.seq
	GTAGCTGC	CCACGG	ATAGTAAT	CGTGAAATTAT	TATTTTCCTCTA	464644
		5260	5270		•	ACAG Majority
5251	CTICCTCC	1		5280	5290	5300
5251	GTAGCTGC	CCACGG	A A T A G T A A T	CGTGAAATTAT	TATTTCCTCTA	A C A G cohi_ai2.seq
		CORCGG	A A A G I A A I	CGIGAAATTAT	TATTTTCCTCTA	A C A G a909_ai2.seq
	GTTATACT	TCCCAGI	T G C T T T T.T	CCGAACCTTCA	GTTAGAGTTGTA	
	· ·	5310 ·	5320		•	A I A I Najority
rant	CTT4.74.0.7	T	•	5330	5340	5350
5301 5301	GTTATACT	TUUURAG	TTGCTTTTT	CCGAACCTTGA	GTTAGAGTTGTA	ATAT coh1_a12.seq
	o n - n - n - n	ICCCRG		CCGAACCTTGA	G T T A G A G T T G T A	A T A T a 909_ai2.seq
	TCCCTGAT	CCATCAC	TAATAGTT	ACTTCATAACA	TCCTTCGTTCAA	
	•	5360	5370		•	A I C A Rajority
COCI	•			5380	5390	5400
5351	TCCCTCAT	CCATCAC	TAATAGTT	ACTTCATAAGA	CCTTCGTTCAA	ATCA cohi_ai2.seq
		C C A I C, A.C	IXATAGTT	ACTTCATAAGA	TCCTTCGTTCAA	A T C A a909_a12.seq
•	ACTACAGA	AGCAGAT	GGCATAGT	A T C C T T T A T A A A	CATATTGATACA	
		5410			-	CTTT Majority
	14.0.00		5420	5430 ·	5440	5450
5401 5401	A C T A C A G A	AGCAGAT	GGCATAGT	ATCCTTTATAA	CATATTGATACA	CTTT cohl ai2.seg
3401	A-CIACAGA	AGCAGAT	GGCATAGT	ATCCTTTATAA	CATATTGATACA	C T T T a909_a12.seq
					GTAATAGTATAT	
٠.		5400			TAATAGTATAT.	TTGA Majority
		5460.	5470 .	.5480 .	5490	5500
5451	TTCTGTAC	CATGATA	ATTGACTG	CATTC.TT.ATAAC	TAATAGTATAT	T'T G A cohi al2 sen
5451	I C I G I A C	CATGATA	ATTGACTG	CATTCTTATAAA	G T'A A T'A G T A T A T	T T G A a909_ai2.seg
					GTTTTTCCACC	
	· .	5510			GITTTTCCACCA	A C.C A Majority
		:	5520	5530	5540	5550
5501	CTGTATCA	CCAACCG	AGTACGTT	TTTGATCTACA	GTTTTTCCACC	A C C A cohi aiz seg
. 3391	CIGIALLA	CCAACCG	AGTACGTT	TTTGATCTACA	GTTTTTCCACC.	A C C A a909_a12.seg
	TCTCCCCA	T G.T C G C A	TCAGTATTO		AGTAGCATTTG	
		5560			AGIAGCATTEG	A G T Wajority
			. 5570	5580	5590	5600
5551 5551	TCTCCCCA	TGTCGCA	TCAGTATTO	TTTTCATGAAT	AGTAGCATTTG	GAGT cohl al2.seg
3331	TOTOLOGIA	I G I U G C A	TCAGTATTO	C T T T T C A T G A A T	AGTAGCATTTG	A G T a909_a12.seq
					CAGTGCTAGAAA	
		5610-			CAGIGCIAGAAA	LCAT Majority
500.		1	5620	563 0	5640	5650
5601 5601	TACAGATG	TAACCAT	AATMACAGO	TCCATTATTAA	CAGTGCTAGAAA	CAT cohl ai2 sea
3001	LACAGAIG	TAA-CCA.T	AATTA.CAGO	TCCATTATTAA	. CAGIGCIAGAA	C A T a909_ai2.seq
					GTACCATCATTA	
		ECCO				TTT Majority
	 	5660	5670	5680	5690	5700
5651	AATAATAT.	C.CATATT	GGGAAACAT	TAATAACCTCA	GTACCATCATTA	TTT cohl at2 sea
. 2021	AATAATAT	CCATATT	GGGAAACAT	TAATAACCTCA	GTACCATCATTA	TTT a909_ai2.seg
• :						
t				GIAGIAII AGC	TGATATAGATTT	AGC Kajority
		5710	5720	5730	5740	5.750
5701	GACTCAGT	AACAGTG	GAAACTGGT	G.T. A G T A T T A G C	TGATATAGATTT	A C C cohi più con
5701	GACTC'AG.T	AACAGTG	GAAACTGGT	GTAGTATTAGC	TGATATAGATTT	A G C a909 a12 seg
					_	
•			ATTIGETGA	CGCAGTATCTT	TTTTAGTTACAT	A T G Majority
		5760	5770	5780	5790	5800
5751	CCATGTCG	CAATCTC.	ATTTGCTGA	CGCAGTATOTT	TTTTACTTACL	4 7 2
5751	C C A T G T C G (CAATCTC.	ATTTGCTGA	C-G C A G T A T C T T	TTTTAGTTACAT	A T C agon at 2 acc
	TICICCOTO	ATTAG	AGTTGTCG	TAAAAAG.AGAA	TTAAAATCAGTT	G A A Majority
		58io	5820	5830	5840	5850
5801	TTCTCCCTC	CATTAC	CAGTTOTCO		TTAAAATCAGTT	
5801	TTCTCCCTC	CATTAG	TAGTTGTCG	TAAAAAGAGAA	TT A A A A T C A G T T TT A À A A T C A G T T	GAA cohl_ai2.seq
	•	, -			* * A A A A I U A U I I	⊌ н н ав∪э_aiz.seq

Aliana	mord Bonord way to a color to		119/487	
Thurs	ment Report CWO 2006/07 day, July 29, 2004 0.49 FM			PCT/US200
	5860	5870	5880 5890	AGCTCCATC Majority 5900
5851 5851	G C T T A T A C T C A	A G C T T C T T T A C C :	T T G A G G A A T T A A A T A A G A T T G A G G A A T T A A A T A A G A	ACCTCCATC
			CATTATCTATTTCTGCAT	CAAAAACTT Najority
5901	TTTATTCGAATC	5920 CAGATACATTTG	5930 5940 CATTATCTATTTCTGCAT	CAAAAACTT cohl at2 seg
5901	TITATICOXXIC	AGAIACAIIIG	CATTATCTATTTCTGCAT	CAAAACTT a909_a12.seq
	5960	S970	5980 5990	GTAATTGTC Majority
5951 5951	TATATGCTTTAT	AGGTTGCGCCTT	TTTCACTATCTTCAACT	CTAATTCTC
			TTTTGAGTATCTTGAACT CGGCGTAACTGGTGATAC	•
	6010	6020	6030 6040	6050
6001 6001	C C T G T C T C A G C G C C T G T C T C A G C G	G C A A A A G C T A T C	C G G C G T A A C T G G T G A T A C C G G C G T A A C T G G T G A T A C	A G C C A T A C C cohi_ai2.seq
			CCATTGAATCATTTTCT	
COT*	6060 .	6070	6080 6090	6100
6051 6051	AAATGCTAAACT	CGCCACTAACAG	C C A T T G A A T C A T T T T C T C C A T T G A A T C A T T T T C T	TTTTCATTG cohi_ai2.seq TTTTCATTG a909_ai2.seq
		•	GATGAATGATTAATTCA	
6101	AAATCTTTCTCC	6120	6130 6140	6150
6i01.	AAATCTTTCTCC	TAAAATCATATT	GATGAATGATTAATTCA GATGAATGATTAATTCA	TATTTTTT coh1_ai2.seq TATTTTTT a909_ai2.seq
-			TCGTAGAGCTAAAGCTA	AACCAACTA Majority
6151	TCGATAGTATA'A	6170 TATTAATCCTGA	6180 6190 T G G T A G A G C T A A A G C T A	6200-
6151	ICURINGIALAA	INTINATUCTGA	T. G. G. T. A. G. G. T. A. A. A. G. C. T. A. A.	AACCAACTA a909_a12.seq
	GGATATAAATGT	GTGTTCCAATAC 6220	6230 6240	•
6201	GGATATAAATGT	GTGTTCCAATAC	CTCCAGTACTAGGCAAT	6250 CCTGTTCCT cohl al2.seg
6201	GGATATAAATGI	GIGITCCAATAC	CTCCAGTACTAGGCAATT	CTCTTCCT a909_a12.seq
	TTACTGTTAGTA	6270	6280 6290	6300
6251 6251	TTACTGTTAGTA	ATTTTAAAAGTA	TATACTCTACTTCCATC	110011100
			TATACTGTACTTCCATC1	
. •	6310	6320	6330 6340	6350
6301 6301	CTCTTTTATTGG CTCTTTTATTGG	T G T C G C A T T A T T T G T C G C A T T A T T	A C C A T T T T G T T C A A A G G T A C C A T T T T G T T C A A A G G T	AACTCCCG cohl_at2.seq
· · .			CATTTTTAGGTAGTAGGT	
·	6360	6370	6380 6390	6400
6351 6351	TAGAAATCACTA.	A T A C T G A T A T A T A T A C T G A A A T A T	C A T T T T T A G G T A G T A G G T C A T T T T T A G G T A G T A G G T	ACCCTGGA cohl_ai2.seq ACCCTGGA a909_ai2.seq
			TATTTCCTACTGGCAAA	• •
6401	6410	6420	6430 6440	6450
6401	GGGGCCTTTGTC	T C.T'G T'T A G G T A G	T A T T T T C C T A C T G G C A A A T A T T T T C C T A C T G G C A A A	CTGAGGTA cohl_a12.seq CTGAGGTA a909_a12.seq
		•	<u>GCCTTTATCGTTTGTCAC</u>	CAGCCCTG Majority
6451	GTTATTAGCATCA	6470 C. A. C. T. A. T. A. C. A. A.	6480 6490	6500
6451	GT-TATTAGCATC	CACTAATAACAA	G C C T T A T C G T T T G T C A C G C C T T A T C G T T T G T C A C	CAGCCCTG coh1_a12.seq
			•	

-	AATAGAT"A"G"GAT GT				
	H min ii & min-min-min	SABE THE PARTY	LUICE ATTAGCA	TCTGATTCATA	AATA Majority :
	6510	6520	. 6530	6540	6550
650		AAGCTTTAT	CCCATTAGCA	TCTCATTCATA	
650	1 · AATÁCATAGGATGTG	AAGCTTTATT	CCCATTAGCA	TCTGATTCATA	A A T A 2000 cl2 cer
	TCAAAACTCCACCT	00-11-11-1			2305_a12.seq
-	TCAAAACTGCACCT	GCTAAAAAA	TATTATCATT	TTCGACATTAA	CTTT Majority
	6560	6570	- 6580	6590	6600
6551		GCTAAAAAA	TATTATCATT		1
6551	TCAAAACTGCACCT	GCTAAAAAA	TATTATCATT	TTCCACA11AA	CTTT cohl_ai2.seq
	CTGTAGTCGTACTTT	TTGCTTGATA	CGTGTATTGG	TAAAGCTAATA	T C T A Majority
	6610 .	6620	6630	6640	•
6601	CTGTAGTCGTACTTT	TTECTTCATA			6650
6601	CTGTAGTCGTACTTT CTGTAGTCGTACTTT	TTGCTTGATA	COTCTATTEG	TAAAGCTAATA	TCTA cohi_ai2.seq
	CGTCTCCTGAAACTG	TCAGGGATTG	TAAGCCGGTA	G C A T C A T A A G T	TTTA Valority
	6660	6670	6680		•
6651	CGTCTCCTCAAACTC			6690	6700
6651	C G T C T C C T G A A A C T G C G T C T C C T G A A A C T G	TMAGGGATTG	TAAGCCGGTA	GCATCATAAGT	TTTA cohl_ai2.seq
	CGTCTCCTGAAACTG				
	TCAGCTTCACCAGTT	GCTAGATTTT	TTTCTGTAAT	T G A C T C A C A T A A	3 T T T W
	6710	6720		• •	LI 1 Majority
6701			6730	6740	6750
6701	T C A G C T T C A C C A G T T T C A G C T T C A C C A G T T	GCTAGATTTT	TTTCTGTAAT	TGACTCAGATA	CTTT cohl_ai2.seg
••••	TCAGCTTCACCAGTT	GCIAGATTTT	TTTCTGTAAT	TGACTCAGATA	CTTT a909_ai2.seq
	AAATTCATCGTAGGC				
	6760			CAGIICCATAAC	GTA Majority
0000		6770	6780	6790	6800
6751 6751	A A A T T C A T C G T A G G C	TTGTTCATCT	ATTGATAGA	AAGTTCCATAAC	G T A cohl al2 sec
	AAATTCATCGTAGGC	TTGTTCATCT	ATTGATATAGA	AAGTTCCATAA	GTA a909_a12.seg
	CTTTKAATTCCTTAGT	CTGACCATC	T.C.T.C.4.C.C.C.C.4.4		
	6810			CAATICICTCTGT	TGC Majority
		6820 .	. 6830	6840 :	6850
6801 6801		CTGACCATC	TCTCAGCGGAA	AATTCTCTCTTGT	T G C cohl at2 seg
9001	CTTTAAATTCCTTAG	CTGACCATC	TCTCAGCGGAA	AATTCTCTTTT	T G C a909_a12.seq
	AACGTTTCACTTGGAT				
	6860.			TIATETTEATE	TAG Majority
cora		6870	. 6880	6890	6900
6851 6851	AACGTTTCACTTGGAT	TAAACAAGA	AGTCTTTCGTC	TTATCTTCATC	TAG cohl ai2 seg
000 i	AACGTTCACTTGGAT	TAAACAAGA	AGTCTTTCGTC	TTATCTTCATC	TAC a909_ai2.seg
	TCCAACGACAGTTTTA				
	6910			IIIAGGTTGCC	A A A Majority
		6920	6930	6940	6950
6901	T.C.C.A.C.G.A.C.A.G.T.T.T.A.T.C.C.A.A.C.G.A.C.A.G.T.T.T.A	CTTACTCTG	ACGGTGTATTC	TTTAGGTTGCC	A A A cohi al2 sag
	TCCAACGACAGTTTTA	CTTACTCTG	ACGGTGTATTC	TTTAGGTTGCC	A A A a909 a12 seq
	CAGCATATAAGGTATT	TOTICCATE	GGGTTGTTAT	CAATACCTATT	G A T Majority
	6960	6970	6980	6990	7000
6951	CAGCATATAAGGTATT	TGTTGCATCT	GGGTTGTTAT	CAATACCTATE	GAT cohi ota con
6951	CAGCATATAAGGTATT	TGTTGCATC	GGGTTGTTAT	CAATACCTATT	GAT agno at 2 sec
	TGACCTCCTCTCT				s it I abou_arz.seq
٠	TGACCTGCTGTAAATT	CCACACGTCC	TGTATCAGCT	AAATCCTTATC	A T G Majority
•	7010	7020	7030	7040	7050
7001	T G A C C T G C T G T A A A T T T G A C C T G C T G T A A A T T	CCACACCTCC	TOTATOLOGY		و القائميسيم
700L	TGACCTCCTCTAAATT	CCACACGTCC	TGTATCAGCT	AAATCCTTATC	A T'G cohl_ai2.seq
	4 m a a a 4 4 a a a 4 4 4 4 4 4 4 4 4 4		:		wire sana siz.sed
	ATGCCAACCAATAAGG	TTGTAACCTG	TCCTTGTAAA	GTATTGGTTTT	CAG Majority
		7070	7080	7090	• •
	7060			unan .	7100
7051		TTGTAACCTC	TCOTT		
7051 7051	ATGCCAACCAATAAGG	TTGTAACCTC	TCCTTGTAAA	GTATTGGTTTT	C A G cohl_ai2.seq
	ATGCCAACCAATAAGCATGCCAATAAGC	-,, 11 11 00 10	TOCLIGIAAA.	GIATTGGTT.T	CAG a909_ai2.seq
	ATGCCAACCAATAAGCATGCCAATAAGC	-,, 11 11 00 10	TOCLIGIAAA.	GIATTGGTT.T	CAG a909_ai2.seq
	ATGCCAACCAATAAGG	ATTCAACTCC	ATACCCCCTC	CTATTEGTTTT TCTCTACTTGT	C A G a909_a12.seq G T T Majority
٠	ATGCCAACCAATAAGG ATGCCAACCAATAAGG GAATTGTAGTTGTGCT 7110	A T T C A A C T C C	ATACGCGGTG	TCTCTACTTGT	C A G a909_ai2.seq . G T T Majority
7101	ATGCCAACCAATAAGG ATGCCAACCAATAAGG GAATTGTAGTTGTGCT	A T T C A A C T C C	ATACGCGGTG	7140	C A G a909_ai2.seq G T T Majority 7150

Thursday, July 29, 2004 6:49 PM ACCA GAT TACCATTEAT MAJORITY 7160 7170 7180 7190 ACCACATTACCATTTCTACTCTAGTACCACCGTTACCATTGTATTTGAT cohlai2.seq 7151 ACCACATTACCATTTCTACTCTAGTACCACCGTTACCATTATATTTGAT a909_a12.seq 7151 TGAGGTATCTTCTAATTTGATATCTCCTACTGGAATAATGACAGGTTTTA Majority 7210 7230 7240 7250 7201 TG A G G T A T C T T C T A A T T T G A T A T C T C C T A C T G G A A T A A T G A C A G G T T T T A cohl_al2.seq
7201 TG A G G T A T C T T C T A A T T T G A T A T C T C C T A C T G G A A T A A T G A C A G G T T T T A a 909_al2.seq TGGTGATATTTTATTAGCATCTGCTAAATGGGCGTCAATATCAATGGAA Majority 7270 7280 7300 TGGTGATATTTTATTAGCATCTGCTAAATGGGCGTCAATATCAATGGAA cohlai2.seq 7251 TGGTGATATTTTATTAGCATCTGCTAAATGGCGCGTCAATATCAATGGAA a909_a12.seq TCATATGGGTTATAAATTTTACCATTGTACCACCAGCCACGGAAACGATA Wajority 7320 7330 7340 7350 TCATATGGGTTATAAATTTTACCATTGTACCACCAGCCACGGAAACGATA cohlai2.seq TCATATGGGTTATAAATTTTACCATTGTACCACCAGCCACGGAAACGATA a909_a12.seq 7301 GCCATCTGGCATTGTCGGACGTCTCAGTAAGGCTGAATGGGAGCCATCGT. Majority 7360 7370 7380 7390 7400 7351 GCCATCTGGCATTGTCGGACGTCTCAGTAAGGCTGAATGGGAGCCATCGT cohl_ai2.seq.
7351 GCCATCTGGCATTGTCGGACGTCTCAGTAAGGCTGAATGGGAGCCATCGT a909_ai2.seq CATAGGAATCAGGGTCAGTAGGCTCATTACTTGTTAATTGCTGACCA Wajority 7410 7420 · 7430 7440 7401 CATAGGAATCAGGGTCAGTAGGCTCATTACTTGTTAATTGCTGACCA cohlai2.seq 7401 CATAGGAATCAGGGTCAGTAGGCTCATTACTTGTTAGTAATTGCTGACCA a909_a12.seq GAAGCATCCAATGCTGGCTTTCCATCTGTACCAACAGCATCATTGCTGTA 7460 7470 7480 7490 . 7500 GAAGCATCCAATGCTGGCTTTCGATCTGTACCAACAGCATCATTGCTGTA cohlai2.seq 7451 GAAGCATCCAATGCTGGCTTTCCATCTGTACCAACAGCATCATTGCTGTA a909_a12.seq 7451 TATAATATGATAATCTCCAGCCTTTCGCCAAATAGCTCTTAAATTGATAT Hajority 7520 7510 7530 7540 7501 TATAATATGATAATCTCCAGCCTTTCGCCAAATAGCTCTTAAATTGATAT cohlai2.seq TATAATATGATAATCTCCAGCCTTTCGCCAAATAGCTCTTAAATTGATAT a909_ai2.seq CTTGAGTTACAGCACCTGAAAAGTTATAAGGTCTAATACTACCATCTGGA Majority 7560 7580 7590 7600 7551 CTTGAGTTACAGCACCTGAAAAGTTATAAGGTCTAATACTACCATCTGGA cohl_al2.seq
7551 CTTGAGTTACAGCACCTGAAAAGTTATAAGGTCTAATACTACCATCTGGA a909_al2.seq TTAACATACCAACCGACTAATTTGTAAGCGTCTTTTACGTACTTGTA Majority 7630 7610 7620 7640 . 7650 TTAACATAACCAACCGACTAATTTGTAAGCGTCTTTTACGTACTTGTA cohlai2.seq 7601 TTAACATAATACCAACCGACTAATTTGTAAGCGTCTTTTACGTACTTGTA a909 afz.seq ETTAGTTGTATCAACATTTGAGAGACTAGTATCTCTCTATAATAGG Majority 7690 . 7700 CTTAGTTGTTGTATCAACATTTGAGAGACTAGTATCTGTCGTATAATAGG cohl_at2_seq CATCTTTAGTTGAGTCGGGATCTTTATCTCGTGAATCATACTTATAAA Najority 7710 . . . 7720 7730 7740 · 7750 7701 CATCTTTAGTTGAGTCGGGATCTTTATCTCGTGAATCATACTTATAATAA conlai2.seq 7701 CATCTTTAGTTGAGTCGGGATCTTTATCTCGTGAATCATACTTATAAAAAA a909 a12: seq TATGTACCTGAAGGATCTTGGATATAATCCCTTGTAATATCTGTATAATC Majority 7770 7780 7800 7751 TATGTACCTGAAGGATCTTGGATATAATCCCTTGTAATATCTGTATAATC cont_at2.seq TATGTACCTGAAGGATCTTGGATATAATCCCTTGTAATATCTGTATAATC a909_ai2.seq

CGGAAEACGATCACCCATTTCACATTTCACATCTTTTC 7810 7820 7830 CGGAATACGATCACCATAATGCAAGTCTAAATAGGTATCATCTGTTTTTG a909_ai2.seq ATAATTGGCCTCCGTTTGGATCAATATTGACACGATATGTTACCTTTTGC Hajority 7860 7870 7880 7890 7851 ATAAT GGGCCTCCGTTTGGATCAATATTGACACGATATGTTACCTTTTCC cohl_ai2.seq 7900 ATAATTGGCCTCCGTTTGGATCAATATTGACACGATATGTTACCTTTTGC a909_a12.seq CAACCTGCATAGACTTTAACATCATGAGGCCATAGTCGTGTTAAAGTC Majority 7920 7930 7940 7950 7901 CAACCTGCATAGACTTTAACATCATGAGGCATAGTCGTGTTAAAGTC cohlai2.seq CAACCTGCATAGACTTTAACATCATGAGGCCATAGTCGTGTTAAAGTC a909_a12.seq AAATACTTGTGTTTTGGCTTTTATACCATTTACCATCCCAAACAT Hajority 7960 7980 7990 8000 7951 AAATACTTGTGTTTTGGGTCTTTATACCATTTACCATCCCAAACAT cohl_al2.seq 7951 . A A A T A C T T G T G T T T G T G C T T G G T C T T T A T A C C A T T A C C A T C C C A A C A T a909_a12.seq ACCCTGGTCGACTAGGTTTAGGTTGAACCGTTGTCGTATCGGGGGCATAA Majortty 8010 8020 8030 8040 - 8050 ACCCTGGT.CGACTAGGTTTAGGTTGAACAGTTGTCGTATCGGGGGCATAA cohl_al2.seq 2001 ACCCTGGTCGACTAGGTTTAGGTTGAACCGTTGTCGTATCGGGGGCCATAA a909_a12.seq 8001 GAGGACAAATTTTGCTCATATAGAACATCCTTTACTGGAAAATTAGGAAG Majority 8060 8070 8090 8080 8100 GAGGACAAATTTGCTCATATAGAACATCCTTTACTGGAAAATTAGGAAG cohlai2.seq 8051 GAGGACAAATTTTGCTCATATAGAACATCCTTTACTGGAAAATTAGGAAG a909_a12.seq 8051 CTCTGTATTATCAAGCGGATCTAAATATTTAATCTTGTATGAATTACGTT Majority 8110 . 8120 8140 * 8130 8150 CTCTGTATTATCAAGCGGATCTAAATATTTAATCTTGTATGAATTACGTT cohlai2.seq 8101 8101 CATACCATACCACTAAGTTCAAATATCTTTGTGGTAGTCTCCATATTTA Majority 8160 8170 8180 8190 CATAC-CATACCACTAAGTTCAAATAATCTTTGTGGTAGGCACCATATCTA cohlai2.seq 8151 8151 TCGTAGTATTCATCTGCGATTGGCACTTTTGTTTTTGCACTCGTTTGTCT Majority . 8220 8230 8240 . 8250 TCATACTATTCATCTGAAATAGGAACTTTTACTCCTGCACTCGTTTGACT cohlai2.seq TGGGTTCTGATCAAATAGGTAATTATCTGGATATAAGCTTTGATAGTATT Majority 8280 8270 8290. 8251 TGCCTACTCATAAAGCTAATTATCACGATATAAACGTTGATAATCACGTTGATAAACGTTTCOhlai2.seq-8251 TGCCTTAGATAGTATTAATCTGGATATAAGCTTTGATAGTATT TAACATTAAATCCTAGGTATTTTTCTGTAAAGGTAAATTCGTCTGGTCCA Majority 8310 8330 8320 8340 . 8350 .8301 TAACATTAAATCCTAAATCCTATATTTTCTGTAAAGGTAAATTCATCTGCCCCCA cohlaiz.seq GCACCTCCCCCTGTGTCTGCTAAAGAGTATTTGCCATCTAGTCCTTGTTT Majority 8360 8370 8390 GCACETCCACCTATCTGCTAAAGAATAAGTGCCATCCAAACCTTGTTT cohlaiz.seq GCACCTCCCCCTATGTCTGATAAAAAGTATTTGCCATCTAGTCCTTGTTT a909_a12.seq GTAGAACGGATAATTTTGAATTCTCTTCCCTTTTGGATAGAGTTTTATTT Majority 8410 8420 8430 8440 CAAGAAC CGATAAGTTTGAACTATATTCCCTTTTGGAAAGAGTTTGATAA cohl al2.seq 8401 ATAGAAAGUATAATTTGAATTCGCCTGACCAAACAGGATAUAATTTTATTT a909_ai2.seq

Aligna	ment Report oWO sday, July 29, 2004 b.	2006/078318納の	method with Weighted r	. 123/48 residue weight table.	7.	PCT/US20
	CATCTGG	ATT TE CT	A T C T A G T C	CATIGGGTAG	TATGAACTCA	C C C A A A Majority
	-	8460	8470	8480	8490	8500
8451 8451	CATAAGG	ATTTCCTCC	ATGTACTC	CATTAGGTAA CATTGGGAAG	A A T G A A C T C A C T A T A A C T C A	C C C A A A cobl_al2.sec
					CAACATTGGT	
		8510	8520	8530	8540	. 8550
8495 8501	TAACTCA	TTCCTCATAGG	T T C C A A C T	T G G T T A T T T C (CAACATTGGC	TAAATA cohl_a12.sec TAGGTA a909_a12.sec
	ACG-CCAT	GCACCTGTC	TTCCATTG	ATAGCCATTC	GCGGCTAAGG	TTGTAC Majority
	<u></u>	8560	8570	. 8580	8590	8600
8545 8536	A C G C C A G	G C A C C C G T C G C A C C T G T C	TTCCATTG	ATANCCATTA ATAGCCATTC	G C G G C C A A G G T	TTGTAC cohi_ai2.sec
					CTAGTTCTAG	
		8610	8620	8630	8640	8650
8595 8586	C G T A A A G C A T A T A G	T C C T G T G T A T C C N G T N T A	AGTATCAC GGTTTCGC	CATCAGA.GC1 CATATGATGC	CTAATTATA CTAGTCAA	GAATA cohl_ai2.seq GAAA C a909_ai2.seq
٠	•		•		TTTTGCAAAT	
		8660 .	8670	8680	8690	8700
8644 8636	G T A A T A T	T T T G G T A A G T T T G A T A A T	GAATATCC AAACCTCA	C C A T A G A G T A G C C C G T	TTTTGCAAA1	TTTAT cohl_ai2.seq
			•		CACTTGAACC	•
	• .	8710	8720	8730	8740	8750
8686 8689	A G T C A C A	A G T T T T C T A K G T T T T C T A	T C A T A A T A A	A A C A T T A A C A A A C A T T A A C G A	CACTTGAACC	ATCGT coh1_ai2.seq ATCGT.a909_ai2.seq
	CTTTTAT	CATGACAGA	AGTTTCTGT	CCTCGTATTA	TTAACTTTAA	A G C C A Majority
	<u> </u>	8760	8770	8780	8790	8800 .
8739 8736	CTTTTATO	C A T G A C A G A C A T G A C A G A	A G T T T C T G T A G T T T C T G T	C C T C G T A T T A C C T C G T A T T A	TTAACTTTAA TTAACTTTAA	A G C C A cohl al2.seq A G C C A a909_al2.seq
					CGTCTGATTA	
		8810	. 8820.	8830	8840	. 8850
8789 8786	GTCGGTA	TTTTCAT	T A A T A T C T T T A A T A T C T T	GTTGTGTTAG GTTGTGTTAG	C G T C T G A T T A C G T C T G A T T A	GATAA cohl_ai2.seq GATAA a909_ai2.seq
	AGATAGGC	CTGATCGT	GTTACTTGC	CCTGCGTACT	CATATGTCTT	TTGCG Majority.
8839		8860	8870	8880	8890	8900
8836	AGATAGGO	CTGATCGT	G T T A C T T G C G T T A C T T G C	C C T G C G T A C T	CATATGTCTT CATATGTCTT	TTGCG cohl_ai2.seq TTGCG a909_ai2.seq
•	CATCAGTA	GCATTTTT	TTATCCGT	TGCTGATTGT	TGCCAGTAGT	TTATC Majority
8889	0.4.7.0.4.7.7.4	8910	8920	8930	8940	8950
	CATCAGTA	GCATTTTT	A T T A T C C G T A T T A T C C G T	T G C T G A T T G T T G C T G A T T G T	TGGCAGTAGT TGGCAGTAGT	TTATC cohl all seq TTATC a909 all seq
	GTGTAGGT	TETTTETEC	GGGGGACC	AATGTGCATA	TAGCGTCGTA	TCCTT Kajority
		8960	8970	8980	8990	9000
8939 ·	GTGTAGGT GTGTAGGT	TGTTTGTG(AATGTGCATA	TAGCGTCGTA	TCCTT coht ai2 seq TCCTT a909_ai2.seq
			•		CACTAGCAGC	
		9010	9020	9030	9040	9050
3989 3986	G G T C A A G A G G T C A A G A	CTTGATTA	A A T C A A A G A A T C A A A G	G C T G C C C A C G C T G T C C C A C		TGTGT coh1_al2.seq TGTGT a909_al2.seq
				-	TCATTAGGCT	
		. 9060	9070	9080	9090	ā 100
9039 9036	ACCACCCT ACCACCCT	G C A A A A G T A	TAACCTGG TAACCTGG	CCTCGTTGGA	TCATTAGGET	TAATT cohl_ai2.seq

•					124/487		
3	Alignn Thurso	nent Report of WO 2	2006/078318 in me	athou with Weighted residue			CPCT/US200
		GTCGAnAnGne	9110	ET G.T.T.A.A. C.A.C.A.	GACGAGGTG 9130	CAATATAGGTA 9140	
	9089 9086	GTCGAAGG	CAGGTTGGG	CTGTTAACACA	CGACGAGGTG	CAATATAGGTA CAATATAGGTA	9150 A C cohl_ai2.;seq
						TACGATTCTTT	
ş	9139	TCCTGTTC	9160 GATAAGTCG	9170 CCTGTGTTGAA	9180 TTCAACACCG	9190 ** TACGATTCTTT	9200
•	9136			C.T.G.T.G.T.G.A.A	TTCAA.CACCG	TACGATTCTTT	A A a909_a12.seq
		A U R C A G G A	9210	9220	9230	T G C T T G A A T T T (C_T_Wajority 9250
	9189 9186	A G A C A G G A	A T A A A G A C T T A T A A A G A C T T	ATGTCTGAAG ATGTCTGAAG	ATACAGGTAA ATACAGGTAA	T G C T T G A A T T T	C T cohi_ai2.seq C T a909_ai2.seq
:		GATTCAGA		*.		AACCTACAAAT	
	9239 9236	GATTCAGA	9260 A A G T G G A G C	9270 TCCATTTGA	9280 GTTTTAGACC	9290 AACCTACAAAT.	9300 A A cohl_ai2.seq
•	5230					A A C C T A C A A A T .	
	289		9310	9320	9330	9340	9350
	286	TAATGTT	G Å A G T G G G T G	GTGAAAGTTT GTGAAACTTT	A A A T G A A C T T A A A T G A A C T T	A A T C C G C G G T T	r C cohl_al2.seq r C a909_al2.seq
		CGTTTCCT	GAACTATCC 9360	AATGGTACTT 9370.	GATAACGCTC	C A A A A T A C T T T T 9390	CA Majority 9400
	339 336	CGTTTCCT	GAACTATCC	AATGGTACTT	GATAACGCTC	CAAAATACTTT; CAAAATACTTT	mil. F:A. oobl ol2 ooo
		•				TACTCATAAAT	
9	389	CCAGCAGA	9410 A T C A T C A T A	TAAAGTTACT	9430 G T C G C C A C T T	TACTCATAAAT	9450
9	386	CCAGCAGA	LATCATCATA	TAAAGTTACT	GTCGCCACTT:	TACTCATAAAT	G G a909_a12.seq
	h <u>.</u>		9460	9470	9480		9500
	439 436	A C G A A C A T	AAATTTCTT	TTGTCTCAGT TTGTCTCAGT	TACAGTTATT TACAGTTATT	G G C T C A C C A A A 7 G G C T C A C C A A A 7	T cohl_ai2.seq T T a909_ai2.seq
•		TAACAGGG	T C A C C A T A C 9510	TTTC.CAGTAG 9520	TAGGATCATA (GGTATACCAACC	
	489 486	TAACAGGG	TCACCATAC	TTTCCAGTAG	TAGGATCATA	9540 G G T A T A C C A A C C G G T A T A C C A A C C	9550 A cohl_ai2.seq
•				•		CTTCTCCTAGAG	
. 9:	539	TTAAAATG	9560 :	9570 T.T.T.A.A.T.C.G.T.C.	9580 G.C.A.A.T.C.C.C.A.A.A	9590 C.T.T.C.T.C.C.T.A.G.A.G	9600
	536	TTAAAATG	CTCTCCTGC	TTTAATCGTC	GGAATCCCAAI	CTTCTCCTAGAG	A a909_a12.seq
•		TICICCAT	9610	9620	9630	9640	A Majority 9650
	589 586	TTCTCCAT	CTTTTATAA CTTTTTATAA	TTTGATGATG TTTGATGATG	A A C T T G C A T A C	C T G A A G C T G T C C T G A A G C T G T C	A colil_ai2.seq A a909_ai2.seq
		G G A A A T T A	-			T A A G T T A A C C T	A Majority
	339	GGAAATCA	9660 TAATCAGTT	9670 CCGTCATTAT	9680 FTTGAAAATG	TAAGTTAACCT	9700 _1_ 'À coh1_ai2.seg ·
	536	GGAAATTA	TAATCAGTT	CCGTCATTAT	TTTGAAAAATG	T A A G T T A A C C T G G A G A A T G A A T	A a909_a12.seq
-			9710	9720	9730	9740	750
	589 586	G G A A C T T C G G A A C T T C	T G T A T T A T C T G T A T T A T C	C T C T T G A A C A . C T C T T G A A C A .	ATTGCATAAA1 ATTGCATAAA1	T G G A G A A T G A A T T G G A G A A T G A A T	C cohl_al2.seq C a909_al2.seq
							•

- 2		•		125/487	
Alignm	ent Report of W lay, July 29, 2004	O 2006/078318 _{1 m}	nethod with Weighted resi	idue welght table.	PCT/US20
		A A A G d A A CIA	TO A CIT GIC TA	GT T T C T T A G T T T C T G C A G T	ATCTT Majority.
0720	TATTT	9760	9770	9780 9790	9800
9739 9736	TGTTTT	A A A A G C A A C A	TCACTGCTA	G T G T T C T T A G T T T C T G C A G T G T G T T C T T A G T T T C T G C A G T	FATCTT cohl_a12.seq FATCTT a909_a12.seq
	TAGATT	TTAATACTTC	TGTTTGACC	A T C A T C T T T A A A G T G A A C A A	
		9810	9820	9830 9840	9850
9789 9786	TAGATT	T T A A T A C T T C T T A A T A C T T C	T G T T T G A C C .	A T C A T C T T T A A A G T G A A C A A A T C A T C T T T A A A G T G A A C A A	CTTTA cohi aiz seg
	AGGTTT	•		G C T T. A T C A T A G T T G A C C T C T	ACTTT Majority
9839	AGGTTT	9860 TCATCTGAAG	9870	9880 9890 G C T T A T C A T A G T T A A C C T C 1	9900
9836		TCATCTGAAG	CTTCTAATG	G C T T A T C A T A G T T G A C C T C 1	ACTTT cohl_ai2.seq ACTTT a909_ai2.seq
•	TACTGG	•	TCTGCTTCT	TTACCATTTGACTCAATAG1	AATGT Majority
. : 9889	TACTCC	9910	9920 T.C. T. C. C. T. T. C. T.	9930 9940	9950
888ė	TACTGG	A G C T T G G G G T G G C T T G G G G T	TCTGCTTCT	T T A C C A T T T G A C T C A A T A G T T T A C C A T T T G A C T C A A T A G 1	AATGT coh1_a12.seq AATGT a909_a12.seq
	CATAGA	GTTTGAAGTT	TTTGATTTC	A C T A T C T T G T T T A G C A A C T T	CTGTC Majority
nona.		9960	9970	9980 9990	10000
9939 9936	CATAGA	GTTTGAAGTT GTTTGAAGTT	TTTGATTTCI	A C T A T C T T G T T T A G C A A C C T A C T A T C T T G T T T A G C A A C T T	CTGTC cohl_ai2.seq CTGTC a909_ai2.seq
	AATGCT	TTTTCTTAT		AGTAGCTGAATTGTCTTT	AATTC Najority
9989		10010	10020	10030 10040	10050
	AATGCT	TTTTTCTTAT	AGTCTTTAA	A	AATTC cohl_a12.seq AATTC a909_a12.seq
•	CGTCAC	CTTTAAATCA	G C A T T T T A C	GGAATCTTAGCTTCTTTGGT	C A A A G Majority
10000	0.0 7.0 430	10060	10070	10080 10090	10100
	CGTCAC	CTTTAXATCA	GCATTTTAC	G G A A T C T T A G C T T C T T T G G T G G A A T C T T A G C T T C T T T G G T	CAAAG a909_a12.seq
	TCACTG			CTAAACATCAATGGTTCTT	CACGG Wajority
10089	TCACTG	, 10110	10120 C.T.C.T.C.C.A.C.C.T	. 10130 . 10140	10150
10086		TTACAGTATA	G T C T G C A C C 1	C T A A A C A T C A A T G G T T C T T C C T A A A C A T C A A T G G T T C T T	CACGA cohi_ai2.seq CACGG a909_ai2.seq
	TAAGCAG	CTTCCTCAG	AGATGATGT	TTCTGTTACACTAGAAGCA	GGAGT Majority
10120	TA 1 C C 4	10160	10170	10180 10190	10200
40400	TAAGCAG		A	T T T C T G T T A C A C T A G A A G C A T T T C T G T T A C A C T A G A A G C A	
	CTGTGG	ттестетес	CAACACTTG	A T T G A G A A C T A G A T G T T G A	T G A A G Majority
		10210	10220	10230 10240	. 10250
10186 10188	CTGTGG	CTTGCTCTGC CTTGCTCTGC	CAACACTTG CAACACTTG	ATTGAGAACTAGATGTTGA ATTGAGAACTAGATGTTGA	T G A A G cohl al2 seq T G A A G a909_al2 seq
	TTACCT	G C T A G A A T T 1	<u> </u>	AAAGTAATCCCCACATCAT	C T G T C Majority
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10239	TT	G G C T A G A A T T 1 G G C T A G A A T T 1	T T A T T T T C T T T A T T T T C T	`	C T G T C cohl_ai2.seq C T G T C a909 ai2.seq
		•		TAGAATTAAAAAATAAGTC	• •
		10310	10320	10330 10340	10350
10289 10286	TTAGTT1	CTTCAACTGT	TATTGCTGG	TAGAATTAAAAAATAAGTC TAGAATTAAAAAATAAGTC	GTTAA cohl_ai2.seq GTTAA a909 ai2.seq
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10339	AAAAGTT	GTTAGGATC	TCAATGACC	A C A T G A T A A T T T T C C Á C T C A C A T G A T A A T T T T C C A C T C	TTTAG cohi_ai2.seq.
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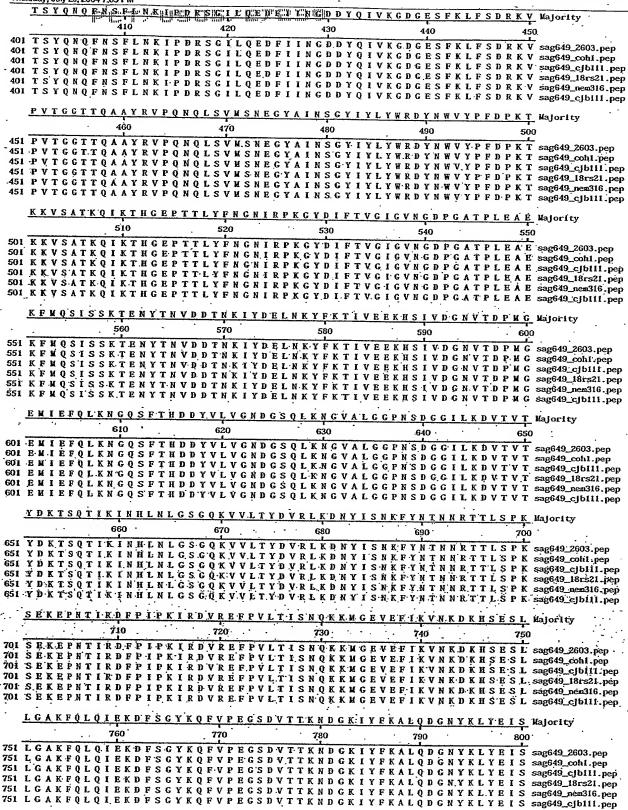
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Alignment Report of gbst WO 2006/078318 Thursday, July 29, 2004 6:57 PM FDLLASDGFAYKWTDA CORANT NEN Y TAGEAVTGQPIKLKSHTDGTFEIK Majority 410 430 440 101 F D L L A S D G T A V K W T D A L I K A N T N K N Y I A C E A V T G Q P I K L K S H T D G T F E I K sag645_2603.pep HOI F D L L A S D G T A V K W T D A L I K A N T N K N Y I A G E A V T C Q P I K L K S H T D G T F E I K sag645_a909.pep 101 F D L L A S D G T A V K W T D A L I K A N T N K N Y I A G E A V T G Q P I K L K S H T D G T F E I K sag645 cjb111.pep 101 F D L L A S D G T A V K W T D A L I K A N T N K N Y I A G E A V T G Q P I K L K S H T D G T F E I K sag645_coh1.pep OI F D L L A S D G T A V K W T D A L I K A N T N K N Y I A G E A V T G Q P I K L K S H T D G T F E I K sag645_nem316.pep GLAYAVDANAEGTAVTYKLKETKAPEGYVIPDKEIEFTVSQTSYNTKPTD Majority 460 470 · 480 490 151 GLAYAVDANAEGTAVTYKLKETKAPEGYVIPDKEIEFTVSQTSYNTKPTD sag645_2603.pep 51 GLAYAVDANAEGTAVTYKLKETKAPECYVIPDKEIEFTVSQTSYNTKPTD sag645_a909.pep 51 GLAYAVDANAEGTAVTYKLKETKAPEGYVIPDKEIEFTVSQTSYNTKPFD sag645_cjb111.pep 51 GLAYAVDANAEGT: AVTYKLKETKAPEGYVIPDKEIEFTVSQTSYNTKPTD. sag645_cohl.pep 51 GLAYAVDANAEGTAVTYKLKETKAPEGYVIPDKEIEFTVSQTSYNTKPTD sag645_nem316.pep ITVDSADATPDTIKNNKRPSIPNTGGIGTAIFVAIGAAVWAFAVKGWKRR Majority 510 520 530 540 O1 ITVDSADATPDTIKNNKRPSIPNTGGIGTAIFVAIGAAVMAFAVKGMKRR-sag645_2603.pep OI ITVDSADATPDTIKNNKRPSIPNTCGIGTAIFVAIGAAVWAFAVKGWKRR sag645_a909.pep OI ITVDSADATPDTIKNNKRPSIPNTGGIGTAIFVAIGAAVNAFAVKGMKRR sag645_cjb111.pep DI ITVDSADATPDTIKNNKRPSIPNTGGIGTAIFVALGAAVNAFAVKGNKRR sag645_cohl.pep D1 I TV D'S A D A T P D T I K N N K R P S I P N T G G I G T A I F V A I G A A V M A F A V K G M K R R sag645_nem316.pep T. K D · N Majority 51 TKDN sag645_2603.pep 51 TKDN sag645_a909.pep 51 TKDN sag645_cjbll1.pep 51 TKDN sag645_cohl.pep 51 TKDN sag645_nem316.pep

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251 A V E K L I D K I T S N K D N R V A L V T Y A S T I F D G T É A T V S K G V A D Q N G K A L N D S V .sag649_cjbiii:pep 251 A V E K L I D K I T S N K D N R V A L V T Y A S T I F D G T E A T V S K G V A D Q N G K A L N D S V sag649_18rs21.pep 251. AVEKLIBKITSNKDNRVALVTYASTIFDGTEATVSKGVADONGKALNDSV sag649 nem316 pep 251 AVEKLIDKITSNKDNRVALVTYÄSTIFDGTEATVSKGVADONGKALNDSV sag649_cfbiii.pep SWDYHKTTFTAT THNYSYLNLTNDANEVNILKSRIPKEAEHINGDRTLY.Q Majority. 320 . 310 . . • . 330 340 301 SWDYHKTTFTATTHNYSYLNLTNDANEVNILKSRIPKEAEHINGDRTLYQ sag649_2603.pep 301 SWDYHKTTFTATTHNYSYLNLTNDANEVNILKSRIPKEAEHINGDRTLYQ sag649_coh1.pep 301. SWDYHKTTFTATTHNYSYLNLTNDANEVNILKSRIPKEAEHINGDRTLYQ 301 S W D Y H K T T F T A T T H N Y S Y L N L T N D A N E V N I L K S R I P K E A E H I N G D R T L Y Q sag649_18rs21.pep 301 S W D Y H K T T F T A T T H N Y S Y L N L T N D A N E V N I L K S R I P K E A E H I N G D R T L Y Q sag649_nem316.pep sag649_cjb111.pep 301 SWDYHKTTFTATTHNYSYLNLTNDANE-VNILKSRIPKEAEHINGDRTLYQ sag649_cjb111.pep FGATFTQKALMKANEILETQSSNARKKLIFHVTDGVPTHSYAINFNPYIS Majority 360 370 380. 390 400 351 FGATFTQKALUKANEILETQSSNARKKLIFHVTDGVPTNSYAINFNPYIS sag649_2603.pep 351 FGATF.TQKALMKANEILETQSSNARKKLI.FHVTDGVPTUSYAI.NFNPYIS sag649_coh1.pep 351 FGATFTQKALUKANEILETQSSNARKKLIFHVTDGVPTUSYAINFNPYIS sag649_cjb111.pep 351 FGATFTQKALUKANEILETQSSNARKKLIFHVTDGVPTNSYAINFNPYIS sag649_18rs21.pep 351 FGATFTQKALMKANEILETQSSNARKKLIFHVTDGVPTMSYAINFNPYIS sag649_nem316.pep 351 FGAT.FTQKALKKANEILETQSSNARKKLIFHVTDGVPTMSYAINFNPYIS sag649_cjb111.pep

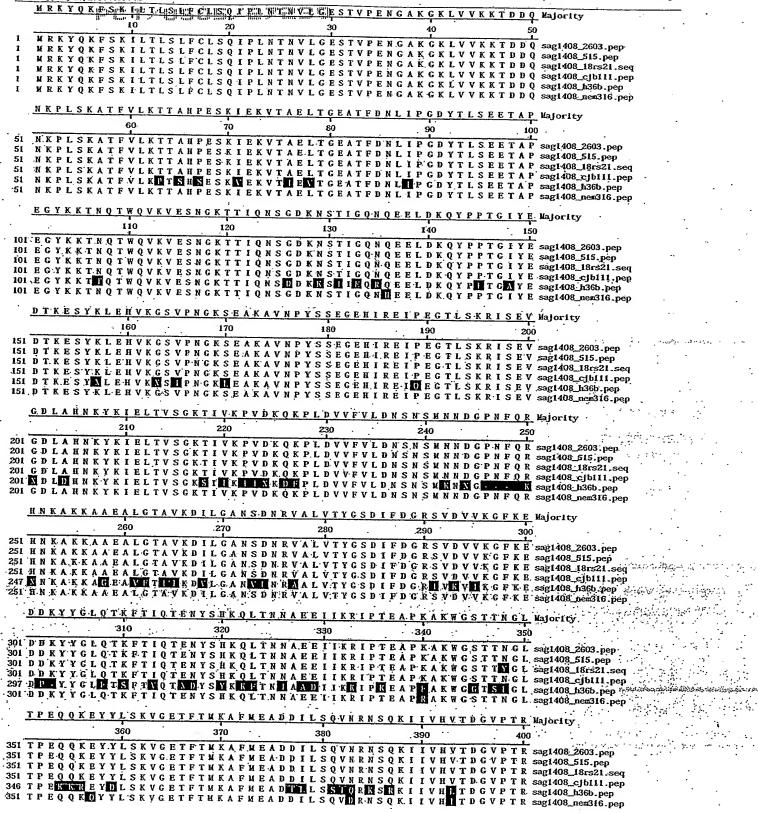


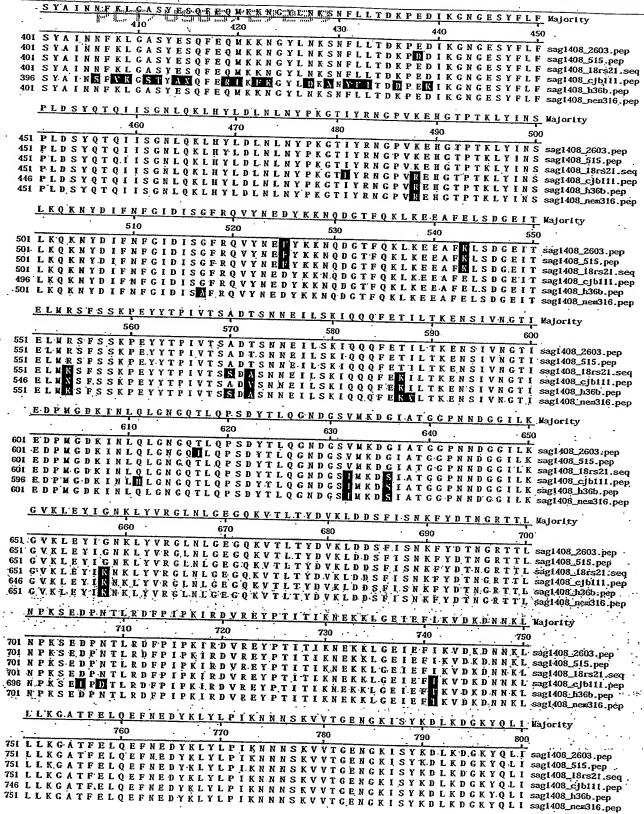
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Decoration 'Decoration #1': Shade (with solid black) residues that differ from the Consensus.

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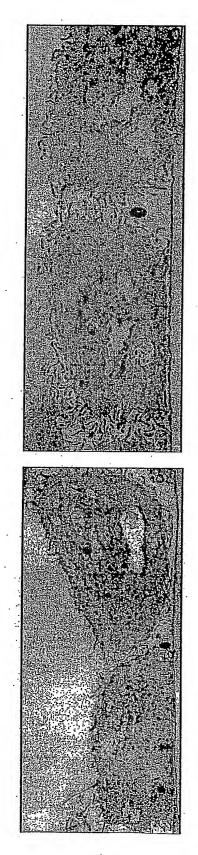
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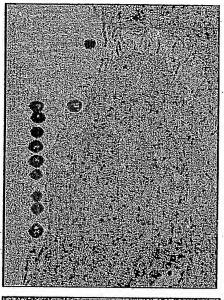
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851 THIPPKGIIPMTGGKGILSFILIGGANNSIAGGIYIWKRYKKSSDNSIKK sag1408_515.pep
851 THIPPKGIIPMTGGKGILSFILIGGANNSIAGGIYIWKRYKKSSDNSIKK sag1408_615.pep
851 THIPPKGIIPMTGGKGILSFILIGGANNSIAGGIYIWKRYKKSSDNSIKK sag1408_61611.pep
866 THIPPKGIIPMTGGKGILSFILIGGANNSIAGGIYIWKRYKKSSDNSIEK sag1408_61611.pep
851 THIPPKGIIPMTGGKGILSFILIGGANNSIAGGIYIWKRYKKSSDNSIEK sag1408_666.pep 900 Majority 901 D sag1408_2603.pep 901 D sag1408_515.pep 901 D sag1408_18rs21.seq 901 sag1408_cjb111.pep 896 ·D sag1408_h36b.pep 901 sag1408_nem316.pep

Decoration 'Decoration #1': Shade (with solid black) residues that differ from the Consensus.

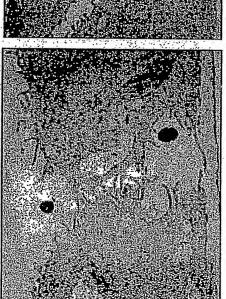
perausosaass

Figure 25: GES closely associate with tight junctions and cross the monolayer by a paracellular route

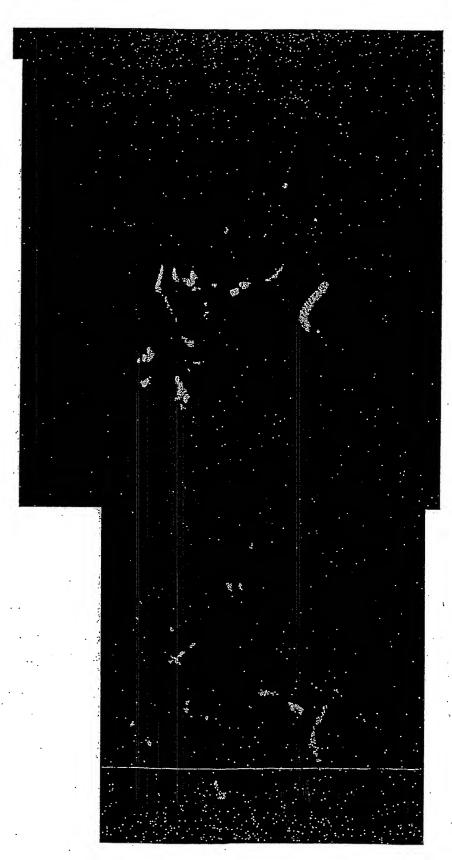


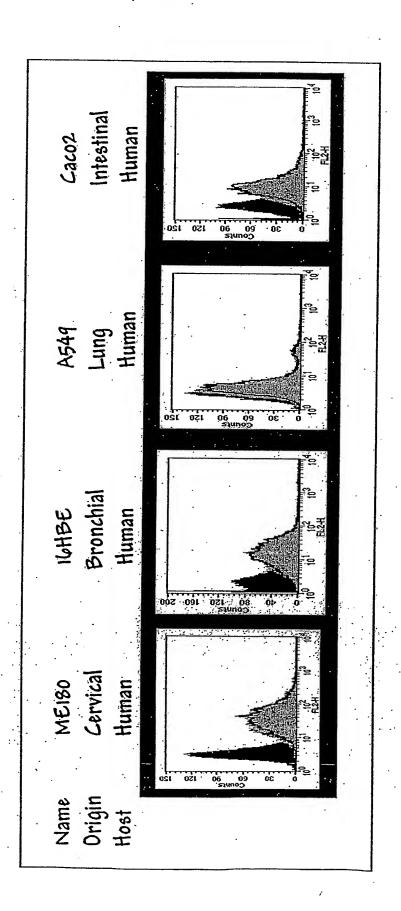






Transmission Electron Microscopy images of GBS infection of ME180 cervical epithelial cells.





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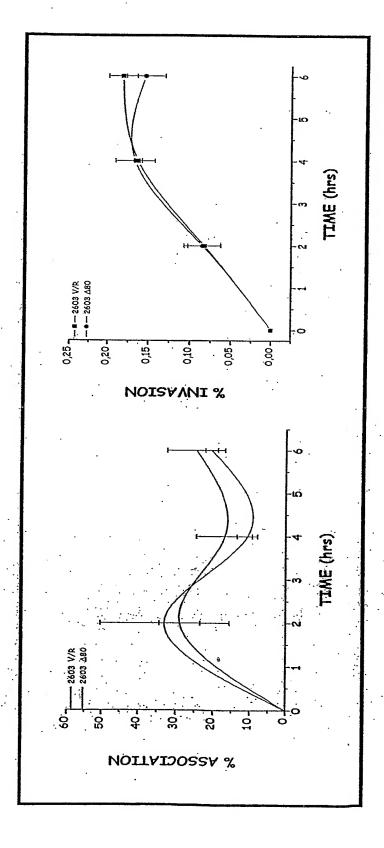
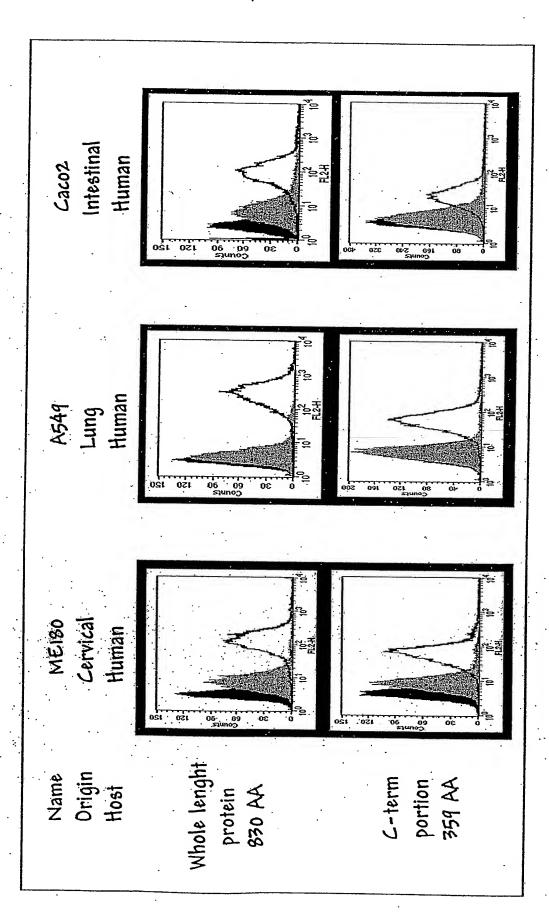
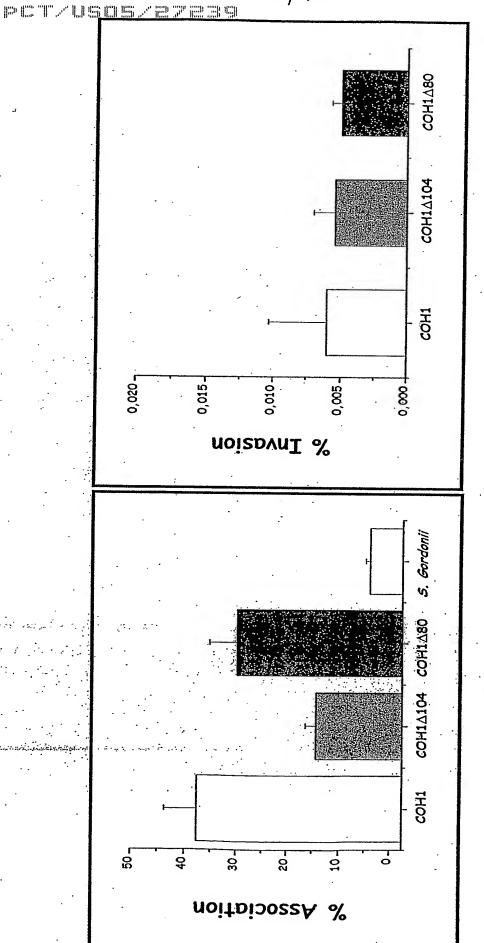


Figure 29

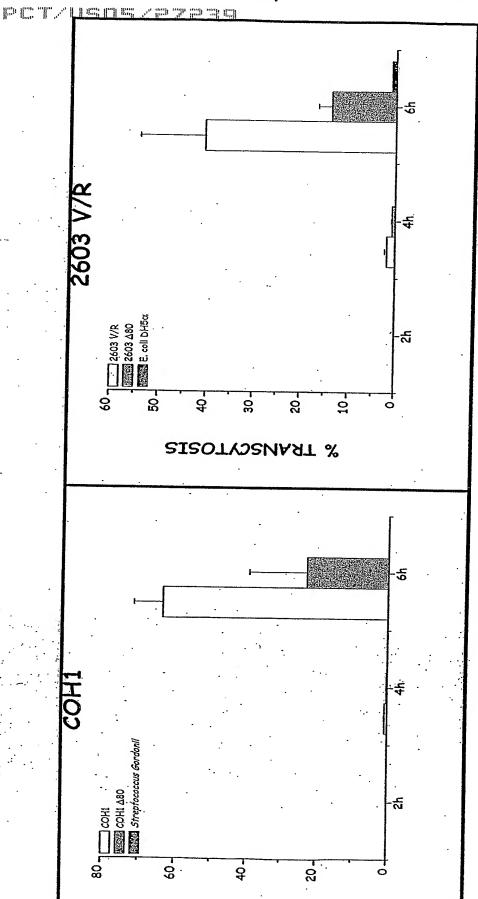




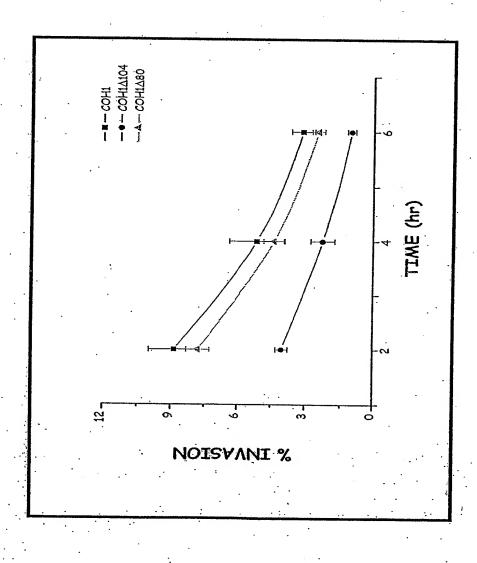


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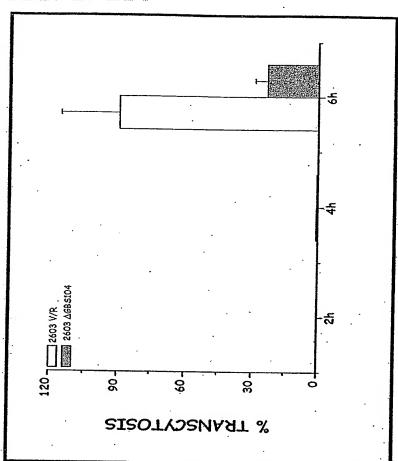


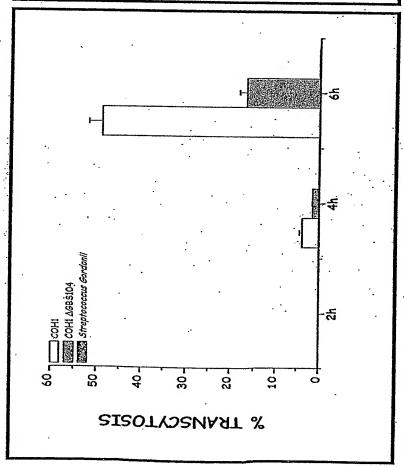
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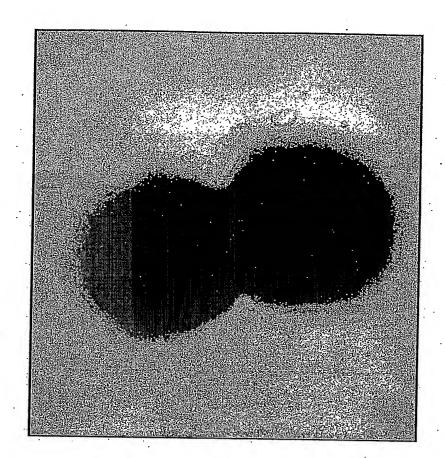


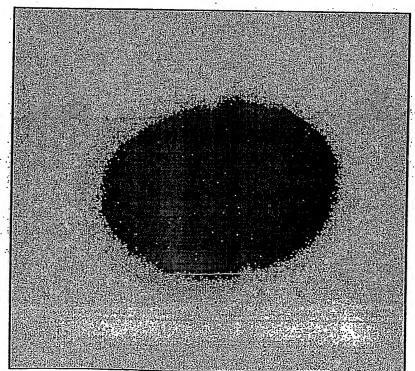


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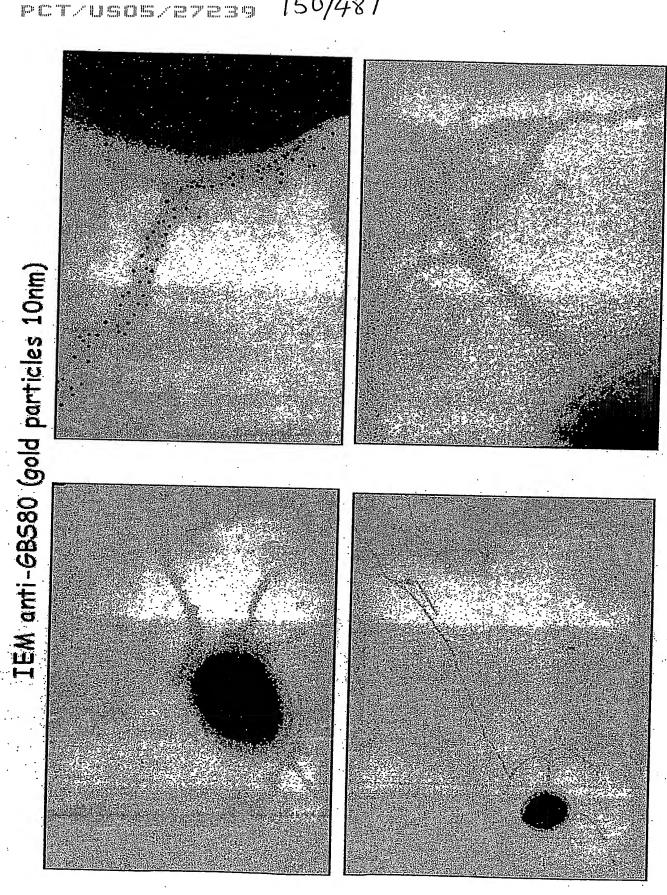
GBS STRAIN COH1 over GBS80

Negative staining EM

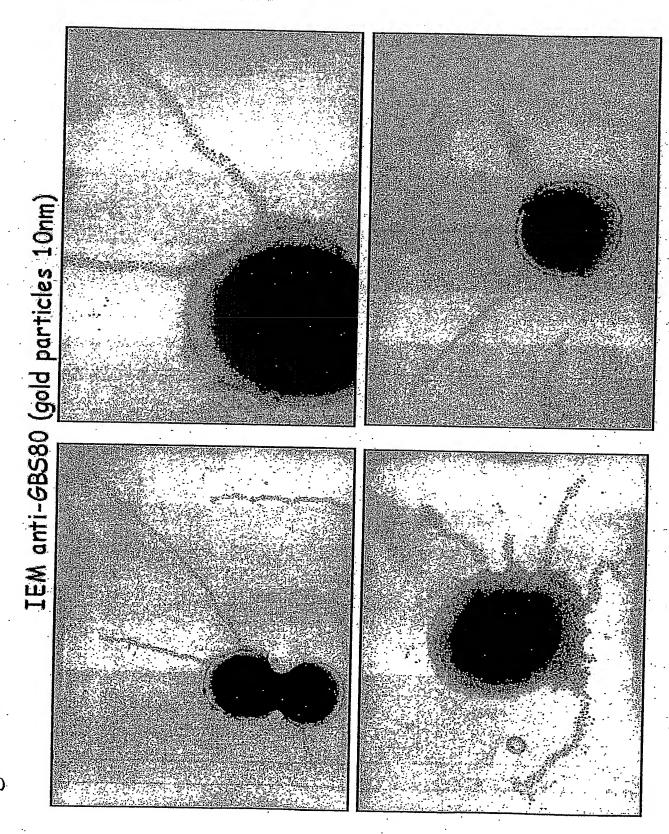




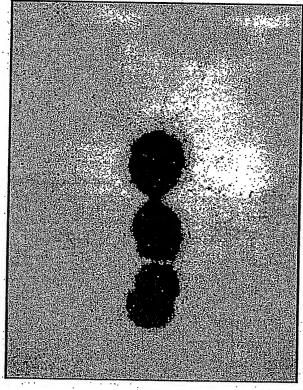
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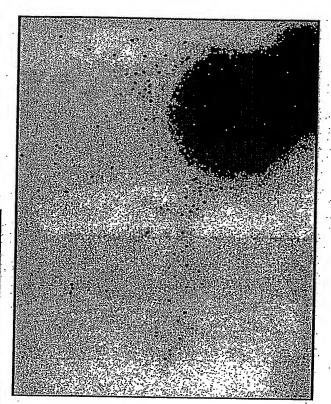


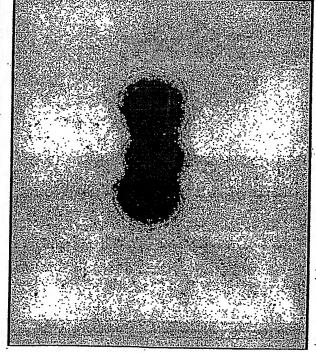
6BS STRAIN COH1 over 6BS80



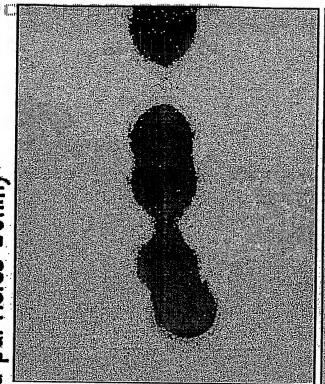
GBS STRAIN COH1 over GBS80 IEM anti-68580 (gold particles 20nm)

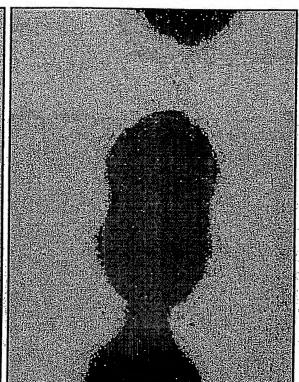


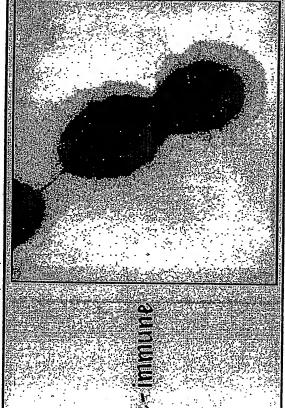


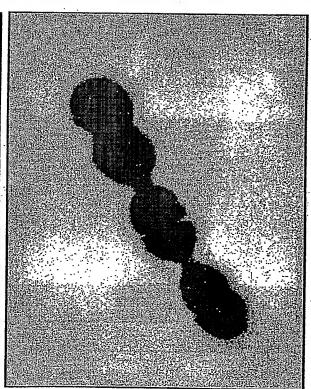


IEM anti-6BS104 (gold particles 10nm)





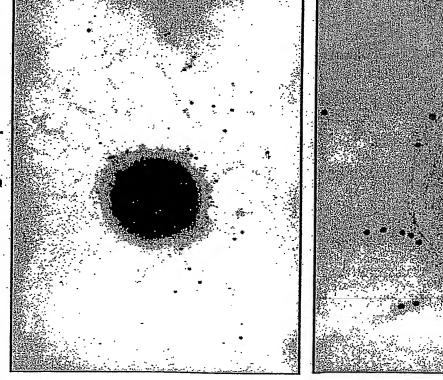


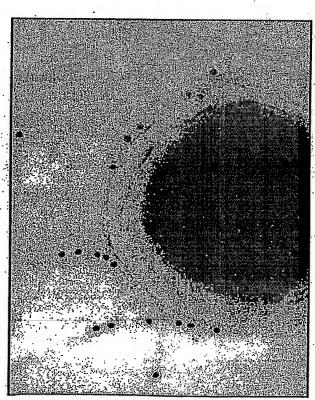


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6BS STRAIN COH1 over 6BS80 Figure 39

IEM anti-6BS80 (gold particles 20nm) anti-6BS104 (gold particles 10nm)

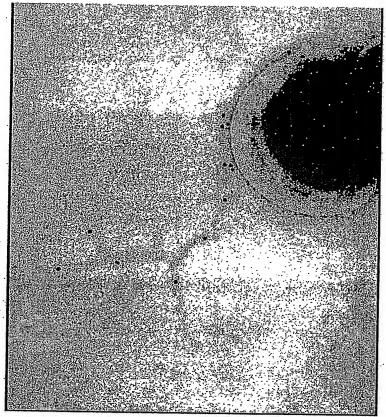




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Figure 40 GBS STRAIN COH1 over GBS80 [gold particles 20nm] anti-6BS104 (gold particles 10nm)





a-Gbs104

Figure 42: Gbs67 is part of a second pilus: Gbs80 is polymerized in strain 515 (515 lacks sortase 647-8, but has AI-2 sortases) 088930 212 212 088950 12/5 212

240 kDa + 14 subunits of

 $Gbs80 = \sim 1000 \text{ kDa}$

Figure 43: Two macro-molecules are visible in Cohl at Conservative size estimate: >1000 kDa, one is the Gbs80 pilin Copi (12x) Designation of the second of t 081 Cohi

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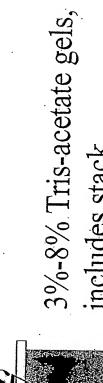
Figure 44

K, TPXIIG

YPK(x₁₀)K

LPx

Figure 45: Gbs52 is a minor component of the GBS pilus



includes stack Left: α -gbs80 Right: blot stripped and reprobed with α -gbs52

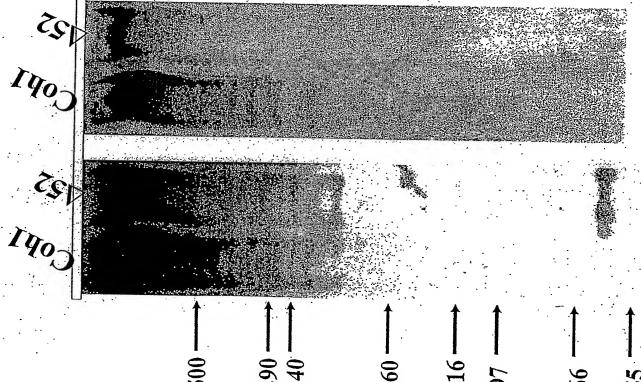


Figure 46: The pilus is found in the supernatant of the bacterial culture

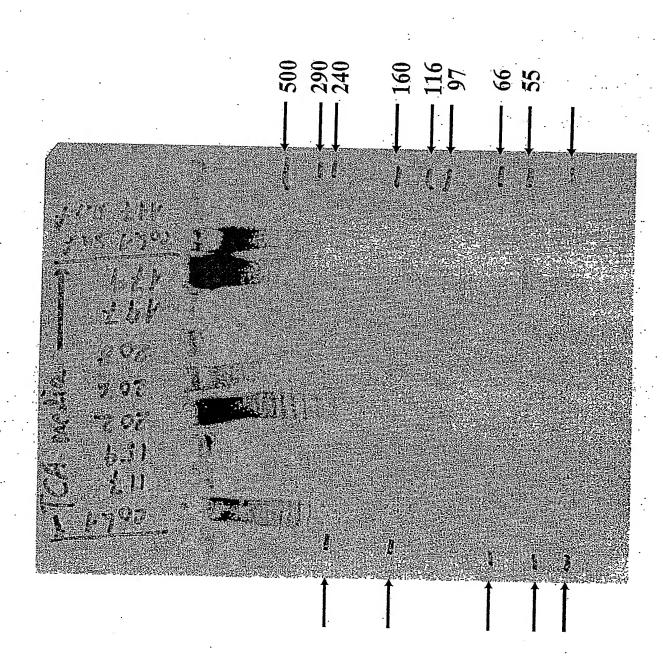


Figure 47: The pilus is found in the supernatant of cultures in all growth phases

TCA precipitation of 1 ml of THB culture supernatant run on 3-8% SDS-PAGE.
OD600 nm are noted above samples, "f" indicates supernatant was filtered (0.2 µM syringe filter).

Left five samples: Coh1.

Right five samples: 179 (AGbs80/pGbs80).

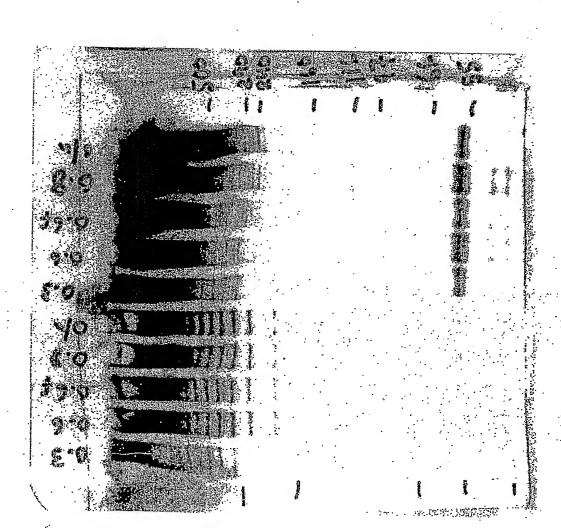


Figure 48: In Cohl, only the gbs80 protein and one sortase (sag0647 or sag0648) is required for polymerization

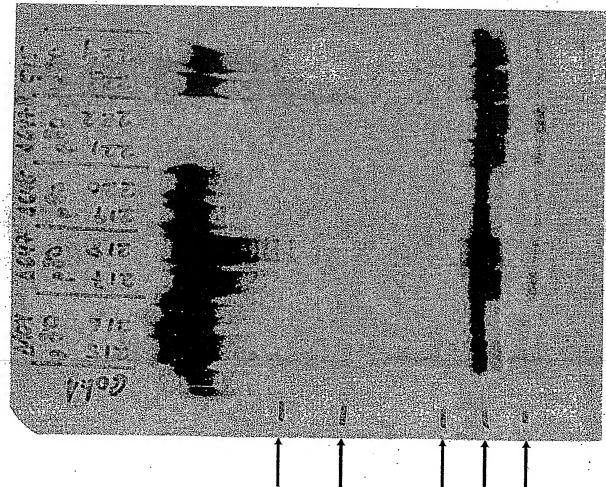
Over expression of gbs80 in various

Over expression of gbs80 in variou strain backgrounds (two clones each).

Total protein extract preparations.

Only the double sortase mutant does not polymerize gbs80.

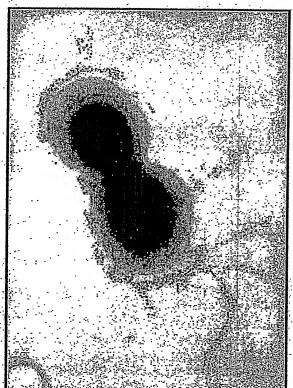
Gbs80 is polymerized in the DK515 strain background (lacks adhesin island 1, adhesin island 2 is 2603-like). Presumably, sag1405&sag1406 are responsible for polymerization.

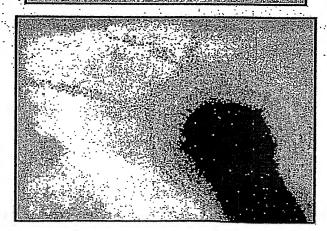


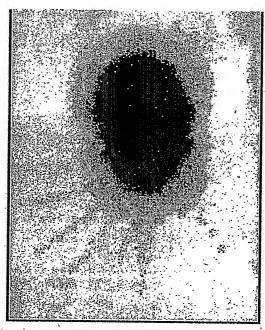
185 STRAIN TM 4030013 IEM amti-64580

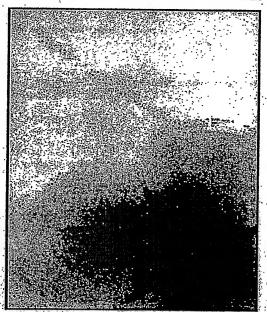
PCT/USOS/87239

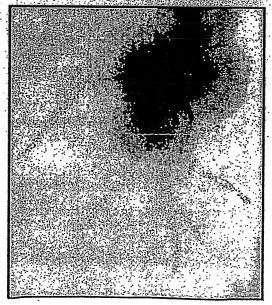


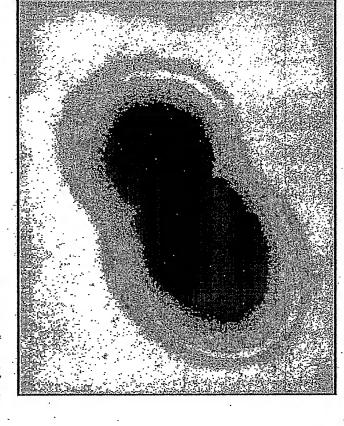


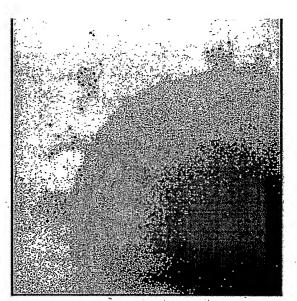


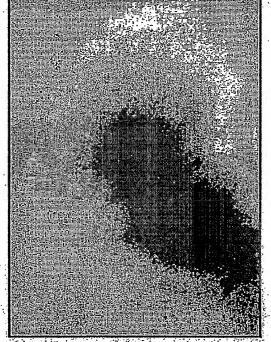


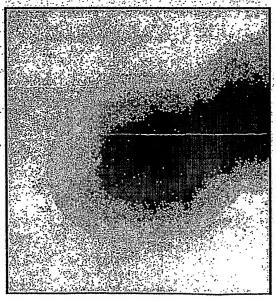




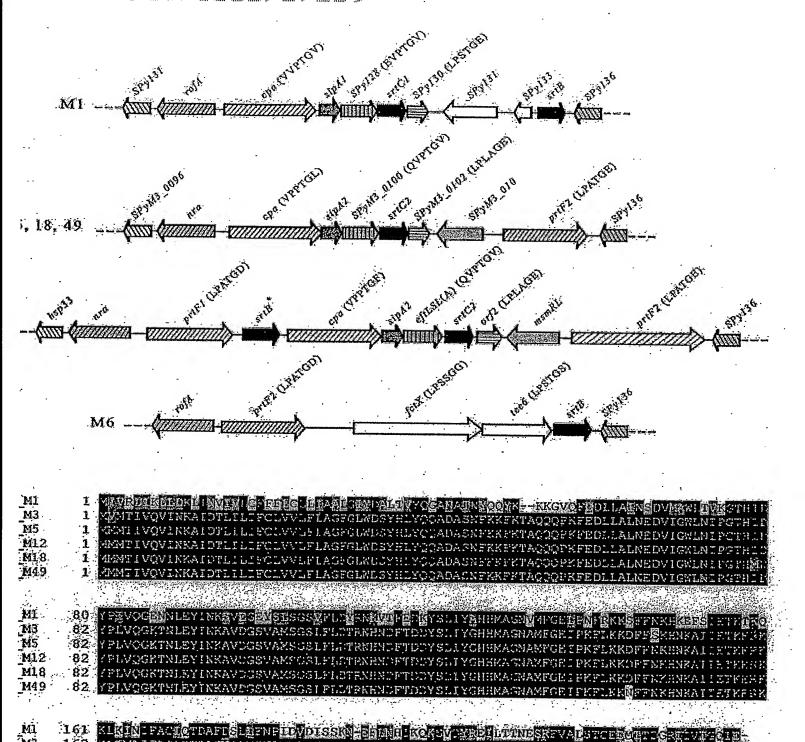












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KLTVT1 FACTSTDAFDQLVFNPNA / TNQ. CQEQLV1YI ŠKPŠKQ FKPVKLK SHTKFVA FSPCENFST DNKV; VVG:

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163

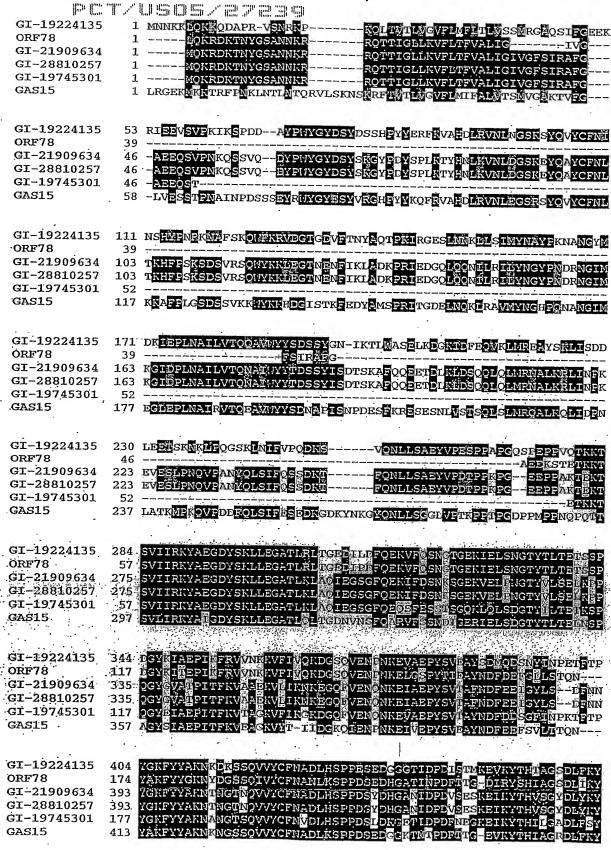
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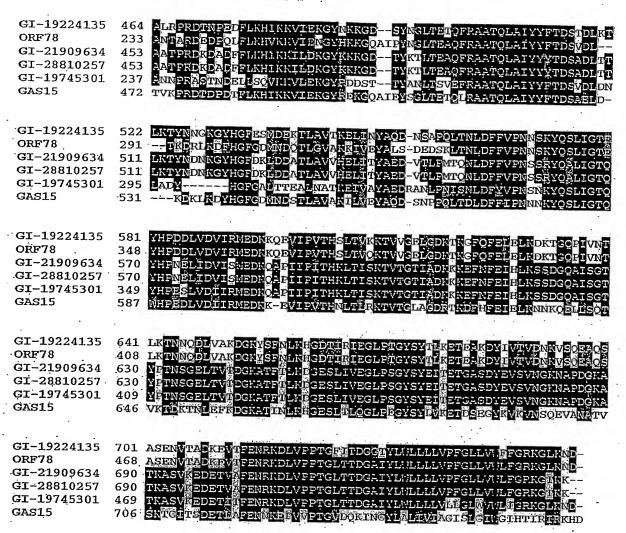
163

М5

M12

M1.8





169/487 PCT/US2005/027239 GI-19224134 61 AADEKTVFNFKSFDPDYPHYGYDSY-----RGIFARYHNLKVNLKGSKBYQAYCFNFTK GI-50913503 61 AADEKTVFSHSSPNPEFPWYGYDAYGKEYPGYNIWTRYHDLRVNLNGSRSYQVYCFNLQS GI-19224134 115 YEERPTYSTTNIEKKIDGSCSAFKSYAANPRYLDENLDKLEKNILNYTYNGYKSNANGE GI-50913503 121 NAPSQKNSFIKNWEKKIBGNCKSFVDYAHTTKLGKE---ELEQRULSHYNEYPNDANGY GI-19224134 175 MNGIEDLNAILVTONAILYYSDSAFLNDVNKMIEREVRKGEISESQVTLMREALKKLIDP GI-50913503 178 MKGEEHLNAITVTOYAVVHYSDNS-QYQFETLESEAKEGKISRSQVTLMREALKKLIDP GI-19224134 235 NLEATAANKIPSGYRLNIFKSENEDYONLLSAEYVPDDPPKPGDTSEHNPKTPELDGTPI GI-50913503 237 NLEATAVNKIPSGYRLNIFBSENEAYONLLSAEYVPDDPFKPGETSEHNPKTPELDGTPI GI-19224134 295 PEDPKRPDESSEFALPPLMPELDGEEVPEVPSESLEPALPPLMPELDGEEVPEVPSESLE
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